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PRIMARY CARCINOMA OF THE LUNGS*

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BOSTON

It is commonly taught that the lungs are very rarely the seat of a primary carcinoma. According to Ewing,[1] it occurs in about 1 per cent. of all cancers.

Adler,[2] whose monograph on primary tumors of the lungs is so much quoted, claims that in reality it is not as rare as is believed. He cites statistics given by Hansemann, who found 711 cases of carcinoma among 7,790 routine necropsies, 156, or 21.94 per cent., of which were not diagnosed antemortem. Of the latter, sixteen, or 10.3 per cent., were bronchial and pulmonary tumors. Adler[2] himself compiled from the literature, up to 1912, 372 authentic cases of primary carcinoma of the lungs.

Of 1,400 necropsies performed during the last ten years at the Peter Bent Brigham Hospital, cancer was diagnosed in 136 instances. Of this number, only five were found to be primary in the lungs. For the same period of time, carcinoma (surgical and postmortem) was diagnosed in the same hospital 784 times. Therefore, the relation of primary lung cancer to all cancers at the Peter Bent Brigham Hospital is 1 : 157.

Of 16,047 necropsies performed in a large Petrograd hospital in ten years, Lawrinowitch[3] found sixty-one, or 0.38 per cent., primary carcinoma of the lungs.

Ménétrier[4] reported six cases of primary lung cancer among 2,500 necropsies performed.

At the Bellevue Hospital (New York City), during a period of twelve years (1907-1919), there were five primary lung tumors found at necropsy.

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* From the department of pathology, Harvard University Medical School and the pathologic laboratory of the Peter Bent Brigham Hospital.

1. Ewing: Neoplastic Diseases, Ed. 2, 1922, p. 808.
2. Adler: Primary Malignant Growths of the Lungs and Bronchi, New York, 1912.
3. Lawrinowitch, quoted by Scott, E., and Forman, J.: Med. Rec. **90**:452 (Sept. 9) 1916.
4. Ménétrier: Traité de Médecine, Brouardel, Gilbert et Thionot, 1917.

Cottin, Cramer and Saloz [5] found in the Cantonal Hospital at Geneva, Switzerland (Hôpital Cantonal de Genève), twenty-nine cases of primary carcinoma of the lungs in a period of twenty years.

Of the number of 13,367 necropsies performed at the Pathologisch-Anotomischen Institut der Universität Innsbruck, Marchesani † found twenty-six cases of cancer (0.2 per cent.) which arose in the bronchi.

It is of interest to note that whereas Cottin, Cramer and Saloz [5] found only twenty-nine cases in twenty years, they were able, later, to discover in one year eight new cases. At the Bellevue Hospital, St. George [6] discovered, in a period of twenty months (1919-1921), seven new cases of primary new growths of the lungs.

Of the five cases mentioned above from the Peter Bent Brigham Hospital, two occurred in 1921, two in 1923 and one in 1924, while during the years 1913-1921, since the foundation of the hospital, no cases of primary carcinoma of the lungs were noted.

The increase in the number of primary lung cancers in the last few years is attributed by some workers to changes in the lungs, resulting from epidemic influenza.

Because of the similarity, from the clinical point of view, of primary lung cancer to any chronic lung affection, and more especially to chronic tuberculosis, a good number of these patients used to be, and are still, directed to tuberculous sanatoriums (Cases 6 and 8) where postmortems are not frequently performed. We believe the increased attention to carcinoma in general, and to lung tumors in particular, to be responsible for the increase in the last decade in the reports concerning this condition.

HISTOGENESIS

There are three elements in the lungs which may give rise to a primary carcinoma: (1) the epithelium lining the bronchial mucosa; (2) the mucous glands, and (3) the epithelium lining the alveoli.

Pathologically, the three types of carcinoma are distinguished according to the gross findings and the type of cells. In rapidly growing tumors, however, the type of cells is not always a reliable criterion for the differentiation. In such cases, the combination of the clinical history, gross anatomy and histologic structure will furnish a "reasonably certain and acceptable" classification (Ewing).

In general, carcinoma arising from the bronchial lining has an alveolar arrangement and is composed of squamous or cylindrical, nonciliated cells. In gross, the bronchial epithelium, the pleura and the parenchyma are usually involved.

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† Marchesani: Frankfurt Ztschr. f. Path. **27**:158, 1924.

5. Cottin, E.; Cramer, A., and Saloz, M. C.: Ann. de méd. **8**:435, 1920.
6. St. George, G.: Proc. N. Y. Path. Soc. **21**:65, 1921.

In tumors originating in the mucous glands, the structure microscopically imitates that of the mucous glands. The cells occasionally secrete mucus, and the bulk of the tumor is usually confined to the submucosa, producing early signs of bronchial stenosis.

Tumors arising from the epithelium lining the alveoli are divided by Ewing into (*a*) diffuse and (*b*) multiple and nodular. In the diffuse form, one whole lobe, or the whole lung, is uniformly consolidated, the lesion resembling organizing pneumonia or gray hepatization in croupous pneumonia. The pleura is usually involved, and local and general metastases are frequent. In the diffuse and nodular form, the air vesicles are completely or partially filled with cuboidal, cylindrical or flat cells.

ETIOLOGY

Clinical observation and experiments favor the theory that cancer is due to a chronic irritation. The development of epithelioma in areas subjected to roentgen rays, epithelioma of the lip of pipe smokers, and the soot, coal, tar and paraffin cancers are widely known.

As regards primary carcinoma of the lungs, Ménétrier affirms that "there is no primary lung cancer without a previous chronic inflammation." Statistics regarding the seat of carcinoma of the lungs and the predominant incidence in the male sex tend to confirm Ménétrier's opinion. According to Adler's statistics, the right side is the favorable location of the new growth. This is explained by the anatomic structure of the right bronchus, which is shorter, wider and more vertical in direction than the left, and therefore more prone to the penetration of foreign bodies and particles leading to irritation and inflammation. The male sex, more exposed in general to lung infections, is also more often affected by primary lung tumors. Of Adler's 372 cases, 209, or 71.9 per cent., occurred in men. In the ten cases reported here, only one occurred in a female as compared with nine in males.

Ewing believes that the tubercle bacillus is the commonest irritative factor. "The chief etiological factor of carcinoma of the lungs," says Ewing, "is tuberculosis."

The coexistence of tuberculosis and carcinoma in the same patient, whether in the lungs or in other organs, has provoked a great deal of discussion. Rokitansky (1876) affirmed that there is an antagonism between the two affections, a belief which was soon denied by a number of reports demonstrating the opposite. Furthermore, it has been shown that both affections may exist, not only in the same subject but in the same organ, whether lungs, mammary gland or uterus.

The dermatologists were first to describe the implantation of an epidermoid carcinoma on top of a lupus vulgaris, the tuberculous origin of which is beyond any doubt. It is of interest to note that in the great majority of cases, the new growth developed in the scar of a

healed lupic lesion, the scar serving as a starting point for the proliferation of the epithelium with the ultimate transformation into malignancy. In Débonnet's [7] series of ninety cases of lupus vulgaris, forty-seven developed epithelioma in the scar.

Is tuberculosis the chief etiologic factor in primary carcinoma of the lungs?

Of 6,536 postmortems at the Pathological Institute at Breslau, Lubarsch [8] found tuberculosis in 2,668, one hundred and seventeen of which, or 4.4 per cent., had cancer, and of the 3,868 nontuberculous cases, 452, or 11.7 per cent., had cancer. From the foregoing figures, it may be said that cancer is almost three times as frequent in nontuberculous cases. (This may possibly be accounted for by the fact that the percentage of nontuberculous patients reaching the "cancer age" is higher than that of tuberculous patients.)

In Marchesani's † twenty-six cases of primary bronchial cancer, the new growth was in connection with cavities in nine instances, two of which were of bronchiectatic nature, and seven of tuberculous. In no instance, however, could the author find any etiologic relationship between the two conditions.

In Adler's [2] series of 372 cases of primary carcinoma of the lungs, there were only nineteen cases, or 5.1 per cent., with tuberculosis. Cottin, Cramer and Saloz [5] and Cramer and Saloz [9] reported thirty-seven cases of primary carcinoma of the lungs, six of which were tuberculous, of which two (Cases 19 and 27) developed apparently on top of a tuberculous lesion (in the wall of a cavity and in the scar at the apex). In nine cases here reported, not a single case showed evidence of a pulmonary tuberculosis.

The French clinicians Martin and Colrat [10] reported, recently, two cases of primary carcinoma of the lungs, the cause of which they believe to be syphilis.

While, in the first case described by the authors, the specificity of the lung infection was evidenced by the presence of a syphilitic gumma, and the relationship between the two conditions is suggestive, in the second, it is rather doubtful (no Wassermann test was done). The writers base their belief on the opinion expressed by Tripier [11] that the alveolar formations lined with a cuboidal epithelium found in a sclerosed or bronchiectatic lung which were present in this case are *new* forma-

7. Débonnet: Lupus et Epithelioma, Thèse de Paris, 1896.
8. Lubarsch, quoted by Claude: Cancer et tuberculose, Actualité medicale, 1901.
9. Cramer, A., and Saloz, M. C.: Rev. méd. de la Suisse Rom. **42**:160 (March) 1922.
10. Martin and Colrat: J. de méd. de Lyon **2**:1049, 1921.
11. Tripier: Traité d'anatomie pathologique, 1901.

tions and are due always to syphilis. This is, however, denied by practically all pathologists, who consider them as normal lung alveoli that have lost their communication with the air passages, with a result that their flat epithelium has undergone a "regressive metaplasia," taking a fetal, cuboidal aspect.

As has been noted, there is a tendency to attribute the recent increase in the number of reports of primary lung carcinoma to the epidemic of influenza, which, as it has been shown, leads to a marked metaplasia of the epithelium of the bronchi and of the alveolar lining (Goldzieher,[12] Askanazy[13]). Myer[14] reported, recently, a primary carcinoma of the lung (metaplasierende karzinom) originating in the epithelium of the right bronchus following influenza. He believes the latter to be the direct cause of the metaplasia which resulted in malignancy.

It will be seen from the foregoing that the chief etiologic factor of primary carcinoma of the lungs is unknown. It is observed that primary carcinoma of the lungs is practically always preceded by a chronic inflammatory process. Tuberculosis, as a chronic inflammation, may account for the origin of a carcinoma leading to a metaplasia of the epithelium (wall of a cavity, scar of a healed lesion) which is ultimately transformed into malignancy. Recent investigations suggest also an etiologic relationship between acute inflammation of the lungs (epidemic influenza) and malignancy.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 45, a book binder, was admitted to the Huntington Memorial Hospital, March 14, 1921, complaining of inability to move the right arm, diplopia and pain in the left eye.

Late in December, 1920, the patient noticed a small, firm tumor, about the size of a hickory nut, in the sacro-iliac region, to the left of the median line. The tumor was not painful on pressure, but he had pain in the sacro-iliac region when he "stooped over." Later, he began to have double vision, with pain and difficulty in moving the left eye, loss of sensation over the left side of the face and loss of taste on the left side of the tongue. His speech became thick, and he made himself understood only with difficulty. He also had slight difficulty in chewing.

Feb. 24, 1921, roentgen-ray examination revealed definite bone pathology in the left ilium near the sacro-iliac joint, consistent with osteosarcoma.

March 2, the patient was operated on at the Cambridge Hospital for a swelling at the junction of the sacrum and the ilium. The pathologic report of the tumor was adenocarcinoma, secondary to some other focus.

The eye symptoms then became progressively worse, and he had greater difficulty in moving the arm. The temperature was 98-101 F.

There was a marked secondary anemia. The erythrocytic count was 1,770,000 per cubic millimeter. The hemoglobin was 45 per cent. The leukocytic count was 13,000 per cubic millimeter. The blood Wassermann reaction was negative.

On physical examination, a few coarse râles were heard in the right intraclavicular region.

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12. Goldzieher, M.: Cor.-Bl. f. Allg. Path. **26**:506, 1918.
13. Askanazy, M.: Cor.-Bl. f. schweiz. Aerzte **49**:465 (Jan. 18) 1919.
14. Myer, Berthold: Frankfurt Ztschr. f. Path. **27**:517, 1922.

March 22, the condition in the right arm was discovered to be a fracture at the upper end of the humerus, apparently through the anatomic neck. During the last few days, the patient had been comatose a greater part of the time. He died after twenty-six days in the hospital.

The clinical diagnosis was adenocarcinoma of unknown origin.

Necropsy.—The necropsy was performed at the Huntington Memorial Hospital by Dr. Goodpasture, twelve hours post mortem. The body was greatly emaciated. A small convex tumor mass, measuring 2.5 by 0.5 cm., attached to the bone but not to the skin, was found over the left temple. There was an obvious fracture at the head of the right humerus. The lymph glands in the left axilla and both inguinal regions were enlarged, discrete and hard. There was no edema. The peritoneal cavity, except for the enlargement of the mesenteric lymph nodes, which contained apparent tumor, was normal.

Thorax: On stripping away the thoracic muscles, definite tumor metastases were found in the fourth and seventh ribs on the right and in the second rib on the left, situated near or in the costochondral junction. These masses evidently involved the medulla and grew through the cortex. When the sternum was removed, it was found to be infiltrated with rather diffuse tumor masses which have grown, especially through the body posteriorly, and there was a large tumor, 4 by 3.5 cm., protruding into the thoracic cavity from the first left rib.

Pleural Cavities: The right lung was free. The left lower lobe was adherent to the thoracic wall by firm, fibrous adhesions.

Mediastinum: The lymph glands draining the left lung were enlarged, firm and infiltrated with tumor. The heart weighed 132 gm., and, except for the small size, was not unusual.

Lungs: The left lung weighed 620 gm. It was quite markedly anthracotic. The upper lobe was air containing and was free, while the lower was adherent to the thoracic wall laterally and posteriorly, and to the diaphragm inferiorly. The inferior lateral two-thirds was firm and nodular. On section, its cut surfaces disclosed a tumor mass, bronchial in distribution, measuring 7 by 3.5 cm., and extending from near the hilum to the pleural surface. The tumor was fairly firm but friable, pale gray with patches of opaque yellow. The lobular structure of the lung, with pigmented septums, persisted in the tumor peripherally, but centrally the pulmonary structure was destroyed. Surrounding the tumor were many gray nodules, apparently peribronchial, giving a wider consolidation of the lung, but not uniform as is the compact tumor. The terminal bronchi were dilated and filled with thick, clear mucus. Some of the consolidated masses showed central softening, leaving small cavities resembling abscesses. The regional lymph nodes were enlarged and infiltrated with tumor. The right lung weighed 355 gm. It was pigmented and air containing. There was no evidence of tumor or inflammatory consolidation in the lung. Larynx, trachea, and alimentary canal appeared normal. The liver weighed 1,180 gm., and contained two tumor nodules, measuring 1.5 by 2 cm. in diameter. The gallbladder was normal.

Suprarenals: The left suprarenal was enlarged by the presence of tumor nodules in the cortex and medulla. The right was normal. Pancreas, spleen, kidneys, urinary bladder, prostate, testes and thyroid gland were normal. The aorta showed a moderate sclerosis of the abdominal portion.

Brain: The fifth nerve on the left side contained a tumor nodule, 0.5 cm. in diameter, situated 1 cm. from the point where the nerve emerged from the brain. No evidence of tumor could be found elsewhere.

Vertebrae: Tumor masses protruded from 0.5 to 1 cm. anteriorly from the bodies of the twelfth thoracic and second lumbar vertebrae. A large abscess filled with gray pus (about 50 c.c.) was situated beneath the left lumbar muscles and communicated with the sinus exteriorly.

Microscopic Examination.—The primary tumor was that in the left lower lobe of the lung. It involved especially the walls of the bronchi which were

infiltrated by tumor cells which had entirely replaced normal mucous membrane in places. From the bronchi, it extended outward into surrounding alveoli. The tumor grew as an adenocarcinoma, and in places the cuboidal or columnar cells may have contained a little mucus. It was judged that the tumor originated in cells of the bronchus. No evidence of cilia were found in the tumor cells. The metastases were quite similar in general appearance and structure to the primary tumor.

The pathologic diagnosis was primary carcinoma of the lung (left) with metastases to the liver, suprarenal, bones (extensive) and fifth nerve, and arteriosclerosis.

The early and extensive metastases to the bones is of interest in this case. The bodies of the involved vertebrae were extensively infiltrated with adenocarcinoma, even though there was no outward change in the structure. It is also of interest to note the invasion by tumor of the fifth nerve and of the lymph glands in the left axilla and in both inguinal regions.

CASE 2.—*History.*—A man, aged 44, an Armenian, entered the Peter Bent Brigham Hospital, March 3, complaining of pain in the abdomen and chest. The family and the past histories were negative. Two and a half months before, he began to suffer from pain in the abdomen radiating to the chest, associated with belching of gas. At the same time, he began to lose weight and strength.

Physical examination showed him to be undernourished and cachectic. The heart was negative. The lungs were normal except for dulness over the left chest anteriorly and diminished breath sounds over that area. In examination of the liver, dulness increased from the fourth space to 6 cm. below the costal margin. The lower border of the liver was distinctly felt. It was smooth, firm and moderately tender. In the median line, just above the lower border, a definite irregularity could be felt in the surface of the liver. The rest of the physical examination was negative.

The blood Wassermann reaction was negative. The stool was positive for bile. Urine examination gave negative results. The hemoglobin was 80 per cent. The erythrocytic count was 5,056,000 per cubic millimeter. The leukocytic count was 9,800 per cubic millimeter. The temperature was 99-100 F.

Roentgen-ray examination of the chest in a lateral position, on admission, showed the tumor mass to arise in the anterior mediastinum. The shadow somewhat overlapped the posterior mediastinum, but the posterior mediastinum was essentially clear.

Roentgen-ray examination of the patient's chest three weeks later showed the progress on the left side to be much more extensive. It involved the whole of the lower lobe region, and there was considerable increase of the density of the root shadows on the right lung.

The patient died after twenty-five days in the hospital.

The clinical diagnosis was lymphosarcoma (?).

Necropsy.—Postmortem examination, performed by Dr. V. C. Jacobson, showed a well developed and emaciated white man with a slight edema of the lower extremities and scrotum. The abdomen was distended and tense. The liver was greatly enlarged, extending about 5 cm. below the costal margin. Its surface was nodular, being covered with a white, pale tumor. The omentum was adherent to the anterior abdominal wall from the umbilicus to the pubis.

Chest: The under surface of the sternum was adherent to the entire pericardium because of the presence of innumerable grayish white tumor nodules which covered the greater part of the pericardium and pleura. The lower third of the pericardial sac anteriorly was not involved in the tumor, but the other two-thirds were covered with a layer of very firm, white tumor, about

12 mm. in thickness. This was continuous with a similar formation over the lower lobe of the left lung to which the parietal pleura was firmly adherent, and which was removed by removing the lung. The middle three fourths of the lower lobe was very firm, and the pleural tumor growth, and that over the mediastinum mentioned, formed a very dense mass continuous from the anterior to the posterior surfaces. The lateral quarter, while showing innumerable miliary to pea-sized nodules on its pleural surface and in its substance, contained a certain amount of air, but the tumor growth was sharply marked off from this zone. The left upper lobe showed numerous pleural metastases and subpleural growths and numerous nodules, from 1 to 1.5 cm. in diameter, in its substance. On section, the growth was densest toward the hilum of the lower lobe, and spread out in a very irregular manner and appeared to originate in a fairly large bronchus which was considerably dilated with a rough, nodular, grayish white tumor growth which proceeded out from this into the surrounding tissue. Pulmonary veins leading from this lung were stenosed 2 cm. from the hilum, and the larger tributaries in the lung were apparently filled with tumor growth. The pulmonary arteries showed also invasion by tumor. The right lung was voluminous and showed fairly marked emphysema. Here and there beneath the pleura could be felt firm, grayish red nodules, the largest 8 mm. in diameter, with contracted, hyperemic borders. The lymph glands along the bronchi and trachea were slightly enlarged; only a very few of them appeared to contain any tumor. The diaphragmatic pleura on the left was studded with small tumor growths, but there was no gross extension through the diaphragm. The liver weighed 6,363 gm. (14 pounds). Its surface was very irregular, due to the presence of innumerable pale white, firm tumor nodules streaked with red, which varied in size from 2 mm. to 8 cm. They formed rounded, rosette-like projections below the capsular level. There was no obstruction of the portal vein, inferior vena cava, hepatic artery or the main trunks of the hepatic vein. Incision longitudinally showed two very large tumor growths in the right lobe, the largest being 19 cm. in diameter. There was very little parenchyma remaining, the tumors being so numerous. In some parts, the location of portal spaces was striking, but it was difficult to ascertain, in the gross, how the tumor reached the liver. Many hepatic veins were invaded, and implantations on the intima were quite numerous in the finer branches. There was some dilatation of the bile ducts, but no remarkable bile staining of the parenchyma and none of the tumor. The lymph nodes at the head of the pancreas and along the bile ducts were found to be invaded by tumor. The other organs, except for the right kidney in which a leiomyoma was found, were not remarkable.

Microscopic Examination.—Lungs: Sections taken from the region of the primary growth showed the following features: The most striking characteristic was the extensive infiltration by the tumor cells, forming a conglomerate new growth. One section showed the alveoli filled with round or oval tumor cells with dark-staining nuclei, and in some areas there was a large mass of necrosis. There was also considerable connective tissue proliferation throughout, and in some areas much small cell infiltration. Some of the blood vessels and alveoli showed a moderate amount of carbon deposit. Many bronchioles and small blood vessels were filled with the same epithelial tumor cells. Lymph glands were firmly adherent to all the surrounding structures and represented a rich tumor cell infiltration with a certain amount of tissue reaction. The section of the bronchiolar wall showed clearly the origin of the tumor. It arose from the epithelium of the mucosa and not from the tubulo-alveolar glands, which, as a whole, were quite normal except for degenerative changes in places, due to pressure of the surrounding tissue. The neoplastic change in the mucosa made the latter about six times its normal thickness. The cells had broken through the muscle wall and between cartilage spaces. The surrounding alveoli were filled with tumor, and invasion of blood and lymph stream had occurred. The small size of the tumor cells was noteworthy. Mitotic

figures were abundant. No ciliated cells were seen. The pleura was greatly thickened. The tumor here was composed of the same type of epithelial cells as the original growth.

Liver: The tumor histology here was similar to that in the lung section. The tumor masses were encapsulated, and the larger ones were undergoing central necrosis. The other organs are not remarkable.

The pathologic diagnosis was primary carcinoma of the lung (left lower lobe, bronchial in origin) with metastases to the pleura, right lung, liver and regional lymph nodes, and leiomyoma of the kidney (right).

In this case, the tumor, originating in the bronchus, gave early metastases to the liver and possibly to the bones. (The patient had pain in the back due apparently to the presence of tumor in the spinal column, which, unfortunately, was not examined.) The new growth was composed of small columnar cells. The unusual increase in size of the liver, due to metastatic tumor was noteworthy (it weighed 6,363 gm.). A remarkable thing in this case was the patient's gain in weight (from 54 to 60.4 kg.), due apparently to the increase in size of the tumors during the last twenty-five days of his life.

CASE 3.—*History.*—A white woman, aged 57, entered the Peter Bent Brigham Hospital, March 14, 1923, with the complaint of pain in the lumbar region extending down the left leg to the knee, inability to walk and weakness of the right hand. The family and past histories were not remarkable. A tumor was removed from the breast twenty-five years before.

Onset of the present illness had been with a dull, persistent, bilateral lumbar pain five months before admission. Two weeks later, the pain extended down the left anterior thigh. There also was trouble in walking and night sweats for from eight to twelve weeks (?), hemoptysis for two weeks, a spoonful in amount.

On physical examination the lungs were essentially negative. The abdomen was spastic, and the left lower quadrant was definitely tender. Several small nodules were found on the left side of the cervix. The blood pressure was systolic 110, diastolic 60.

The hemoglobin was 85 per cent.; leukocytes totaled 7,000 per cubic millimeter; erythrocytes, 5,024,000 per cubic millimeter. The spinal fluid was negative. Urine examination gave negative results. Roentgen-ray examination showed an area of consolidation in the left base.

Following an operation for myoma of the uterus, the wound healed poorly, owing to infection. The patient coughed up blood tinged sputum. The temperature was of a septic character. She died after seventy-five days in the hospital.

Necropsy.—The necropsy was performed by Dr. G. Hansmann. The body was that of a well developed and fairly well nourished, short female. There was an edema of the ankles and legs. The left breast was missing. (There was an operative scar.) The axillary and supraclavicular glands were not palpable.

Pleural Cavities: The pleura on the left side was adherent to the base. On removing the pleura in this region, numerous tumor nodules could be seen in the intercostal muscles and below the periosteum of the rib.

Heart: The heart, except for some warty, recent vegetation at the aortic valve, was not remarkable.

Lungs: The right lung weighed 520 gm., the left, 580 gm. The right lung was literally speckled with small, white, creamy nodules, which varied in size from 1 mm. to 0.5 cm. in diameter. The peribronchial lymph nodes were not enlarged. The left lung contained a large tumor mass in the left lower lobe and in the posterior axillary line just below the interlobar fissure. The two

lobes were adherent by tumor. In this area, the lung was contracted, owing to a tumor growth which caused a puckering of the pleura. On section, the tumor mass radiated into the lung in various directions and was 6 cm. in diameter. On dissecting down the bronchus to the lung, it was found that near the tumor the bronchus was definitely roughened and the tumor seemed to be present in its wall. Along the course of the bronchi and peribronchial lymphatics, numerous tumor nodules could be seen radiating to the root of the lung where very large lymph nodes were found. The largest lymph node measured 5 cm. in diameter. This extended down the posterior mediastinum to the diaphragm. The nodes at the hilum of the right lung were quite normal. The liver weighed 1,335 gm., and was normally plastic and friable. However, it was speckled with tumor nodules, measuring from 2 mm. to 4 cm. in diameter.

Suprarenals: Both suprarenals were enlarged and, on section, thin suprarenal cortex could be seen surrounding grayish tumor masses.

Brain: The brain weighed 1,300 gm. In the left posterior parietal region was a tumor which arose at the site of the longitudinal sinus. It measured 1.5 cm. in length and seemed to extend into the secondary sinuses somewhat. It was definitely adherent to the dura by clot, and its base seemed in places to have infiltrated the dura. When the calvarium was removed, it was found that in the skull, to the right of the frontal bone, was an elevated tumor mass 1 cm. in diameter. When the skull cap was held to the light, it showed areas of increased and decreased density, more marked than one sees in a normal skull, and perhaps evidence of smaller, not very well defined tumors. The first lumbar vertebrae were compressed to 1.5 cm. in width and also apparently contained tumor.

Microscopic Examination.—Lungs: The tumor was made up of columnar epithelium with an oval, vesicular nucleus and a deeply stained nucleolus. The cells had an adenomatous arrangement and were supported by a fine stroma. In sections taken from the bronchi, the tumor showed invasion of all of the coats. The seromucous glands, however, were intact and were surrounded by a thick wall of small, round cells. The circular muscle layer was markedly thickened. The tumor invaded largely the capillaries. An anthracosis was marked in only a few areas.

Suprarenals: In the suprarenals, the tumor closely resembled that of the lungs, while in the liver the stroma was rather abundant and was dense and fibrous.

Brain: The tumor was found as small nodules composed of the cells identical by their shape and arrangement to the new growth. There was an absence of any reaction to the tumor. The brain tissue seemed to have melted away before the tumor. The cells were nowhere ciliated. Mitotic figures were frequent.

The pathologic diagnosis was primary carcinoma of the lungs, metastatic to the brain, bones, pleura, liver and suprarenals.

In addition to the early metastases to the bones, brain and other organs, this case was remarkable by the absence of any lung signs, on physical examination, in spite of the fact that those organs were extensively involved.

CASE 4.—*History.*—A man, aged 55, entered the Peter Bent Brigham Hospital, Oct. 23, 1921, complaining of severe headaches, tinnitis of the left ear, unsteadiness of gait, projectile vomiting, difficulty in talking, hallucinations of death and Bell's palsy. He had always been healthy, up to September, 1921. The family history was negative.

The present illness began suddenly, Sept. 20, 1922, when the patient was brought home from his work with a paralysis of the left side of the face. At the same time, he was disoriented to time, place and person for a few

minutes. Since that time, the patient had been very restless, wandering mentally, and his speech had been thick and hard to understand. A few days later, he developed hallucinations of death, and projectile vomiting.

Physical examination showed an acutely emaciated man disoriented entirely as to his surroundings, time and also as to persons. His face was flushed, and his eyes were bloodshot. The objective findings could be summarized as follows: 1. Restlessness and inability to cooperate. 2. Bilateral blurring of the nasal margins of the disks. 3. Protrusion of the tongue slightly to the left. 4. Marked flushing of the face. 5. Blood pressure—systolic, 160; diastolic, 80. 6. The spinal fluid showing eleven cells and positive for sugar, negative for globulin; the blood Wassermann reaction, negative; hemoglobin, 90 per cent.; leukocytes, 7,800 per cubic millimeter. The temperature was normal. Roentgen-ray examination of the head and sinuses did not show any abnormalities. The patient died after sixteen days in the hospital.

Fig. 1 (Case 4).—Primary carcinoma of bronchus; metastatic tumor lying beneath the cortex at the inferior and lateral aspect of the tip of the occipital lobe.

The impression was that alcoholic psychosis (?) was present.

Necropsy.—The necropsy was performed by Drs. G. Hansmann and F. Fremont-Smith, six hours post mortem. The body was that of a well developed and nourished male. On examination externally, it did not show any pathologic condition. The peritoneal cavity, except for the liver, which contained a few tumor nodules, was not remarkable.

Pleural Cavities: The left cavity contained 300 c.c. of blood tinged fluid. The visceral pleura and the parietal pericardium were studded with tumor nodules. A few nodules were seen in the parietal pleura. The lymph nodes at the hilum were involved by tumor. The pericardial cavity and heart were not unusual. The heart and lungs weighed 1,410 gm. The lungs were uniformly and very thickly studded with hard, gray nodules, 0.4 cm. in diameter. At the posterior aspect of the left lower lobe, the pleura was definitely puckered in toward the hilum. When the lung was cut at this location, a gray tumor mass, 7 cm. in diameter, was brought into view. Some pus could be forced

out of the bronchi on pressure. The liver weighed 1,520 gm., and showed numerous small nodules, the largest being 7 cm. in diameter. A small nodule was also found beneath the serosa of the gallbladder.

Suprarenals: The medulla of each suprarenal was replaced by a firm, gray growth which measured 2 cm. in diameter. The cortex was stretched around it, and appeared normal. The kidneys, except for a large cyst in the left kidney, were not remarkable. The other organs were normal.

Brain: Tumor was found in the floor of the fourth ventricle on the right; in the right lateral ventricle on the surface of the caudate nucleus; beneath

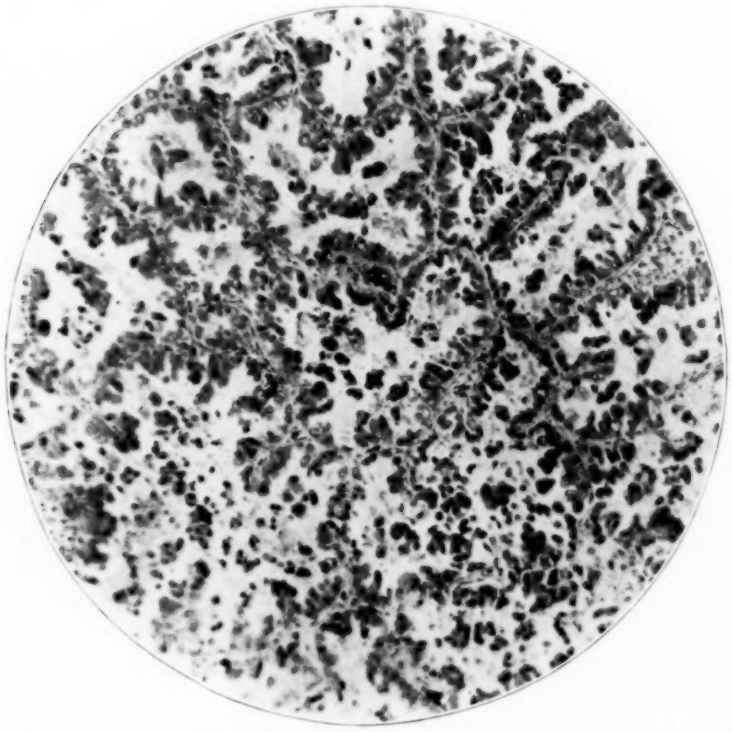

Fig. 2 (Case 4).—Primary carcinoma of bronchus; tumor replacing the lining epithelium of the alveolar wall.

the cortex and at the inferior and lateral aspect of the tip of the occipital lobe (Fig. 1); in the center of the temporal lobe and also beneath the cortex.

Spinal Cord: Lying in the meninges, surrounding the cord at various levels, but most marked at the middorsal region, were firm, whitish plaques, about 1 cm. in breadth by less than 1 mm. in thickness. The meninges were not adherent to the dura or to the cord at these points. Sections of the cord at various levels failed to show intramedullary metastasis. On the posterior surface of the cord, just below the foramen magnum, was a plaque similar to that described, but considerably larger.

Microscopic Examination.—The growth consisted of epithelial cells of the columnar type, supported by a delicate stroma. The arrangement was alveolar

with some projections into the lumina. The cells varied considerably in size and shape, being, however, always columnar with a round or elongated nucleus and a centrally placed nucleolus. Mitotic figures were frequent, especially in the secondary nodules. The growth extended along the lymphatics, which were much dilated. In general, the growth was solid, but in places it seemed to replace the epithelium of the alveolar walls, and free tumor cells were frequently found in the alveoli (Fig. 2). The tumor cells did not contain cilia. The sections showed bronchopneumonia also.

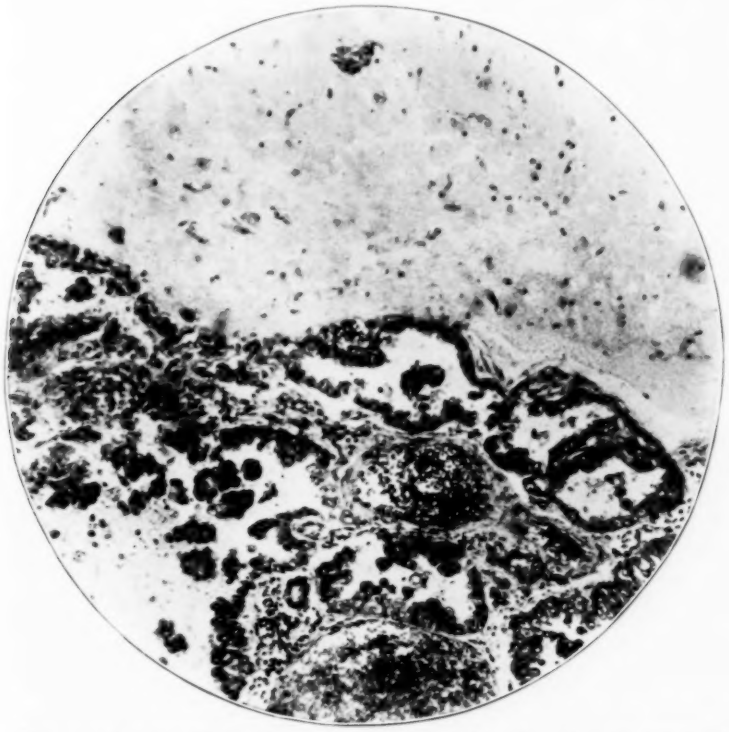

Fig. 3 (Case 4).—Primary carcinoma of bronchus; invasion by tumor of the leptomeninges.

Liver and Suprarenals: The tumor resembled the primary tumor in all respects. The other organs were normal, with the exception of the kidneys which showed infectious nephritis.

Brain: Sections showed the tumor lining large spaces in the leptomeninges (Fig. 3). The tumor cells showed a tendency to arrange themselves about the blood vessels and to invade the cortex along the perivascular spaces. The tendency to so extend was a prominent feature, and the extension was to a considerable depth in places. Several sections showed a quite extensive growth within the cortex with accompanying softening of the cerebral cortex. These growths were usually not far from the meninges and could have communication with the meninges.

Cord: Sections from the cord showed the same type of tumor enveloping the cord. No invasion could be demonstrated.

Dorsal Root Ganglion: The tumor was compact about the nerve roots, and in one place grew right to the edge of the ganglion.

The pathologic diagnosis was primary carcinoma of the lungs with generalized metastases to the brain, leptomeninges, suprarenals, liver and lymph nodes; solitary cyst of the kidney; healed infectious nephritis; bronchopneumonia, and fibrous plaques of the pia arachnoid.

The features of remarkable interest in this case were: The absence of any respiratory symptoms; the sudden onset of the disease with brain symptoms, and the unusually extensive metastases (brain, leptomeninges, pleura, liver, suprarenals and lymph nodes). The tumor grew in solid masses, and in only a few areas the arrangement was alveolar. The cells were columnar, and mitotic figures were abundant, particularly in the metastases.

CASE 5.—(The history lacks details because of the patient's poor knowledge of English and lack of cooperation.) K. L., a man, aged 45, was admitted to the Cambridge Hospital with the complaint of severe headaches and pain in the back and neck. Except for a cough for the last five years, the patient had always been well.

Eight days before admission, the patient began to feel an extreme headache, which had been almost continuous.

On physical examination, the left apex showed dulness with bronchovesicular breath sounds and fine râles. The rest of the physical examination, except for an irregularity of the pupils (the right being larger) and an absence of abdominal reflexes, was negative.

During the stay in the hospital, the patient lost power in the left hand and developed slight stiffness. He died after seven days in the hospital.

A clinical diagnosis was not made.

Necropsy.—The necropsy was performed by Dr. Ash. The body was that of a well developed and somewhat emaciated, white man. The pleural cavities showed the right cavity to be free and the left to be obliterated in the upper third by dense adhesions. The pericardial sac was free.

Lungs: The left lung weighed 1,480 gm. and showed the upper lobe to be the seat of a large, solid mass occupying the entire lobe except for about one eighth of the parenchyma along the anterior border. On section, the mass was solid and light yellow. In the outer portion of the mass, the anatomic lobules were well defined, but the alveoli were apparently completely filled. On the very edge, there were small, scattered nodules, and the intervening tissue was fibrosed with possibly a few remaining uninvolved alveoli. The mass was apparently from one point of origin and had advanced eccentrically and uniformly, reaching the pleura over a large surface, posteriorly and laterally, but not invading it, and the interlobular surface. Here, there were adhesions between the layers of interlobular pleura, but there was no invasion. The pleura was distinctly thickened and, as mentioned, densely adherent, particularly posteriorly.

When the bronchi were dissected to this lobe, the primary bronchus was found to be free, but the upper central division ended after a short distance blindly in the tumor mass. The bronchial mucosa was completely ulcerated, and the presence of the bronchus was determined only by the cartilaginous rings. The adjacent central bronchus was involved by infiltration with tumor, and a smooth, ovoid mass was present in the lumen. From this gross examination, it seemed most probable that the tumor was a carcinoma arising from the mucosa of the upper central bronchus of the upper lobe. The lower lobe was crepitant and free, except for a small nodule in the lower portion posteriorly, involving less than 1 cm. of tissue, apparently metastatic from the

process in the upper lobe. The vessels and bronchi, except as noted above, were free; the bronchial glands on this side were distinctly enlarged, mottled yellow and black. Those under the bifurcation of the trachea also were massive from metastasis. The right lung weighed 860 gm. It was voluminous and congested. The pleura was smooth and glistening. The heart weighed 300 gm. and was normal. The spleen weighed 290 gm. and was enlarged and firm. The gastro-intestinal tract, liver, pancreas and suprarenals showed no pathologic condition grossly. The kidneys weighed, both, 280 gm. and showed no pathologic condition. The pelvises, ureters and bladder were free.

Brain: In the cerebrum, the meninges were not remarkable. The arteries at the base presented a few small plaques of intimal thickening. There were several areas of increased resistance through the cortex. The ventricles were not dilated. On serial section through a horizontal plane, the following tumor masses were found: One was in the right ascending frontal, 1.8 cm. in diameter, involving chiefly the white matter and compressing the gray; it was well defined, light gray with a few fine red mottlings. One was in the ascending parietal, just above the middle, 1 cm. in diameter and 2 cm. long, parallel with the convolution; the upper portion was of a colloid appearance and involved chiefly the white and compressed the gray matter. The third was in the right occipital, 4 cm. in diameter, and involved the white and compressed the gray matter just above the corpus callosum. One was on the left side in the parietal lobe, 1 cm. in diameter, and one on the right side, 1 cm. in diameter, involving the white matter toward the mesial surface. One nodule found in the right side of the frontal lobe was situated in the white matter and touched on the gray matter of the mesial surface.

In the cerebellum, a tumor mass, measuring 1 cm. by 0.5 cm., was found on the right side in the center toward the lower surface.

Microscopic Examination.—Tumor of the Lung: The tumor was made up of a columnar type of cell, usually with an alveolar arrangement, and enclosing masses of cells, more pleomorphic. The cells were not ciliated. There was no mucus. There were great areas of necrosis and fat demonstrated in the necrotic cells. The tumor was extending along the alveolar spaces. The stroma was fibrous and was abundant in some areas. In the less fibrosed areas, the tumor was growing in great masses of cells, having largely obliterated the alveolar structure of the lung. The blood vessels were found to be invaded and thrombosed by tumor cells.

Bronchus: One section from the bronchus, including the upper central branch of the primary bronchus of the lung, showed tumor cells growing in masses, infiltrating the submucosa. The cells here showed much less of the columnar type. Mitotic figures were more common. Another section of the bronchus showed marked infiltration of the wall with destruction of mucous glands and cartilage.

Brain: The cells were of the same type, individually and in arrangement, as those found in the lung. Masses of tumor cells were here supported by a fairly well developed and quite vascular connective tissue stroma. There was considerable necrosis of the tumor in the centers of the larger masses. The striking feature was the lack of reaction in the adjacent brain tissue. For the most part, the tissue seemed to be simply melting away before the tumor. Phosphotungstic acid hematoxylin demonstrated considerable fibrin in the tumor, and there was a small amount in the adjacent brain tissue, but very little glial tissue except along the very edge of the cortex where there was a distinct zone of gliosis. While there were very few glia fibrils, there were a number of the large glial cells, usually necrotic. One section included a cyst in the subcortical tissue containing granular débris and fibrin, and lined with tumor cells, in some places single, in others piled up, particularly about the blood vessels. There was somewhat more gliosis around this lesion than in the more solid nodule. A section from the cerebellum showed the tumor to be identical to the cerebrum tumor.

The pathologic diagnosis was primary carcinoma of the left lung with metastases to the bronchial lymph nodes and the brain, and bronchopneumonia.

The brain symptoms in this case also overshadowed those of the respiratory tract. The tumor in the lungs was apparently of long standing, but, on account of the patient's chronic cough (five years' duration), no particular attention was paid to these organs.

It is remarkable that, in spite of the extensive involvement of the brain (cerebrum and cerebellum), the patient began to complain of cerebral symptoms only about fifteen days before death.

CASE 6.[15]—R. D., a man, aged 37, entered the Boston Sanatorium, complaining of a sharp girdle pain in the right shoulder and right knee. The family history was negative. The patient had neuritis, eight years before, lasting for about three months and ostearthropathy for the last five years.

About three months before admission, the patient began to feel a sharp pain in the right shoulder, followed soon by weakness and loss of weight. Six weeks later, he began to feel pain also in his right knee. He had had diarrhea for the last three months. He coughed very little and expectorated very little sputum.

Physical examination showed a well developed, slightly emaciated man. The chest was asymmetrical, the expansion being diminished on the left side. There was edema of the lower extremities. The cervical glands were palpable. The heart was normal. The lungs showed moderate dulness and bronchial breathing from the apex to the fourth rib on the right side and to the midscapula on the back (right). Bronchial breathing and a few fine râles were heard at the apex on the left side. The abdominal organs and prostate were negative. The bones showed chronic hypertrophic ostearthropathy. The reflexes were normal. The temperature was around 100 F. in the afternoons.

During his stay at the sanatorium, the patient developed pain along the spine and in the forearm. For the last week, he was delirious. He died three months after admission.

The clinical diagnosis was pulmonary tuberculosis; chronic ostearthropathy; blepharitis; tinea versicolor.

Necropsy.—The body was that of a moderately emaciated, white man of tall stature. The upper part of the chest and lower part of the abdomen were covered with branlike scales (tinea versicolor). Just over the inner tuberosity of the right femur, a soft mass was felt which seemed to contain particles of bone. Pleural cavities showed the left to be obliterated by adhesions at the very apex and in the lateral upper portion of the lower lobe. The right was obliterated at the apex and for about 0.5 cm. below laterally. The heart was normal.

Lungs: In the right lung, the pleura was smooth except over the posterior portion of the upper and adjacent upper fourth, where it and the parenchyma were torn in breaking adhesions. The parenchyma was crepitant through the entire middle lobe, the anterior half of the upper lobe and all but the upper posterior fifth of the lower lobe. This excluded tissue was the seat, in the anterior portion, of a uniform infiltration. On cut surface, the tumor was grayish red with small, yellow mottling. It was firm. This tissue was continuous in the two lobes through the interlobar pleura. From the apex was shelled out a well circumscribed, white, firm mass, 1.5 cm. long and 1 cm. in diameter. The tissue behind this firm mass was red, necrotic, rather pultaceous and largely ulcerated away to form a very irregular, indefinite cavity with

15. This case was reported from the point of view of ostearthropathy by Dr. Edwin A. Locke, Arch. Int. Med. **15**:659 (May) 1915.

granular walls and without any fibrous reaction. The overlying parietal pleura was infiltrated with tumor. The ribs were not involved. The remainder of the parenchyma was dark from pigment and richly supplied with blood. The mucosa of the bronchi was deeply congested, the vessels were free and the glands anthracotic. The left lung was voluminous but not heavy. The pleura, except at the apex where it was adherent to the chest wall, was smooth and glistening. The lung parenchyma was deeply pigmented black, generally vesicular and crepitant throughout except for three small masses in the lower lobe. The largest was just beneath the point of the pleural adhesion. The second was located anteriorly toward the base, and the third was deep in the parenchyma. The cut surface of the lungs was dark and moist. The mucosa of the bronchi was congested. The vessels and lymph glands were free from tumor.

Kidneys: The left kidney showed at the upper pole anteriorly a firm tumor nodule, measuring 2 cm. in diameter, which apparently did not involve the medulla. The cut surface of the kidney was generally pale. The cortex averaged 5 mm. The markings were fairly distinct. The right kidney was not unusual. The spleen showed chronic tumor. The liver showed passive congestion. The gastro-intestinal tract was free throughout. The pancreas, suprarenals and prostate were normal.

Knee: In the right knee, the tumor felt through the skin measured 6 by 4 by 3 cm., and was covered by thickened periosteum. It was situated over the site of the inner tuberosity of the femur. This and the adjacent portion of shaft under the tumor were eroded to conform to its shape, and so deeply that the lower portion that the inner condyle was practically a shell. There was considerable loosely clotted blood around the tumor. The latter was not attached to the bone except by periosteum and could be shelled out of its nest in the bone without difficulty, leaving an area of porous bone exposed which was apparently not infiltrated by the tumor.

Head: The posterior end of the left internal orbital convolution was adherent to the orbital plate of the frontal bone for an area 1 cm. in diameter. Where these adhesions were broken, the cortical tissue immediately beneath was soft and white, with small yellow areas of mottling. In the posterior portions of the middle frontal convolutions on both sides were areas of similar cortical softening with this yellow mottling. In posterior portions of the upper frontal on the left side was a soft area but more grayish and without the yellow. These areas were practically all of the same size, i. e., from 1 to 1.5 cm. in diameter. Similar areas of cortical softening also were disclosed in the left middle occipital, posterior tip of hippocampal, left ascending parietal, upper surface, right gyrus fornicatus, right lenticular nucleus, involving a small portion of the middle of the internal capsule, lower end of the ascending, frontal and parietal convolutions that cover the island of Reil and extending into the contiguous cortex of the island, left marginal convolution, lower edge, and, finally, in the tegmentum of the pons.

Microscopic Examination.—The alveolar tissue in the right lung was displaced by tumor which consisted of columnar epithelium, the height of which depended apparently on the amount of compression. These cells formed irregular alveolar-like spaces into which projected papilla-like elements. In areas, the spaces were filled with tumor cells unattached to lining cells, much more irregular in size and shape and showing less the columnar type. There were several spaces lined with young, regular, cuboidal cells, such as are seen in the fibrosed lung, showing only in places the malignant characteristics, penetration and rapid, irregular growth. No cilia could be found on any of the cells. The tumor cells accumulated in the spaces seemed to be rather of a squamous type. In one area, a thick-walled artery was found to contain tumor cells. The stroma of the tumor was of a connective tissue type, was vascular and, in areas, thick with some hyalinization. In the left lung, sections taken from a small tumor nodule showed the growth to be cellular and arranged

in nests, surrounded by a young connective tissue. The predominant type of cell here was squamous. There was in the lungs an inflammatory reaction evidenced by the presence of vacuolated endothelial cells, a number of multinucleated cells and polymorphonuclears. Mitotic figures were present in all sections.

Kidneys: The tumor had an adenomatous arrangement and was composed of cuboidal cells. The stroma was dense and fibrous.

Knee: In the right knee, the tumor consisted of columnar cells having an adenomatous arrangement and squamous cells gathered in nests. There was much necrosis in the sections.

Brain: Sections from four areas of cortical softening showed practically the same picture. The centers of the masses were necrotic; around this was a layer of tumor conforming closely in type of cell and arrangement to those of the parent tumor, i. e., cylindrical cells arranged either in irregular alveolar and acinar-like spaces or forming tubes about the young blood vessels forming part of the tumor. This extension along the arteries was quite striking, practically every vessel (in the tumor area) being completely surrounded by one or more layers of tumor cells. There was an occasional area in which the cells were more atypically squamous-like (Fig. 4). The tumor had its own stroma of connective tissue which in areas formed fairly thick trabeculae, covered by one or more layers of tumor cells. The areas were richly vascuolized, and there was definite penetration into the surrounding brain tissue by small groups of cells. In some areas, the arrangement of young connective tissue and blood vessels resembled granulation tissue. The heart showed focal and chronic interstitial myocarditis. The liver showed chronic passive congestion, and the spleen, chronic tumor.

The pathologic diagnosis was primary carcinoma of the right lung (from bronchial mucosa) with metastases to the left lung, the left kidney, the periosteum of the right femur, and the lymph gland of the right knee; chronic passive congestion of the liver; chronic tumor of the spleen, and ossifying periostitis.

The patient's chief complaint in this case was cough and pain in the chest and pain in the knee, the last due to a metastasis. The brain metastases, as in the previous case, disturbed the patient only a short time before death. Pathologically, this case is of interest in relation to the transformation (metaplasia) of columnar cells in the tumor into squamous (in the left lung). I shall discuss this question in connection with Case 9.

Case 7.—W. C. N., a man, entered the hospital complaining of sore throat. The family and past histories were not obtainable. Physical examination was negative except for local throat signs. After entrance, the patient developed cough and pains in the chest, and raised purulent sputum. A blood culture at that time showed streptococci. The temperature was septic, and the white count increased. The upper third of the right chest showed signs of consolidation. Roentgen-ray examination of the chest suggested either encapsulated empyema, organizing pneumonia or neoplasm.

The patient was operated on. A solid lung was found which was tapped in all directions without obtaining pus. Following the operation, the temperature gradually returned to normal, but cough and pain in the chest persisted. There was a gradual loss of weight and strength, and the respiration became difficult. A Wassermann reaction at this time was positive, and arsphenamin and iodid were given without improvement. Six months after entrance, edema of the right arm and supraclavicular region developed. The patient died seven months after entrance.

A clinical diagnosis was not made.

Necropsy.—The necropsy was performed by Dr. Stoddard. The body was that of a well developed, somewhat thin, but not greatly emaciated white man. There was edema of the right arm and right supraclavicular fossa. The lymph nodes were palpable. The pericardial cavity, the mediastinum and the heart were normal.

Lungs: The left lung was voluminous, emphysematous and contained no consolidated areas. The right lung was adherent from the apex to the upper border of the fifth rib. The part free from adhesions was compressed so

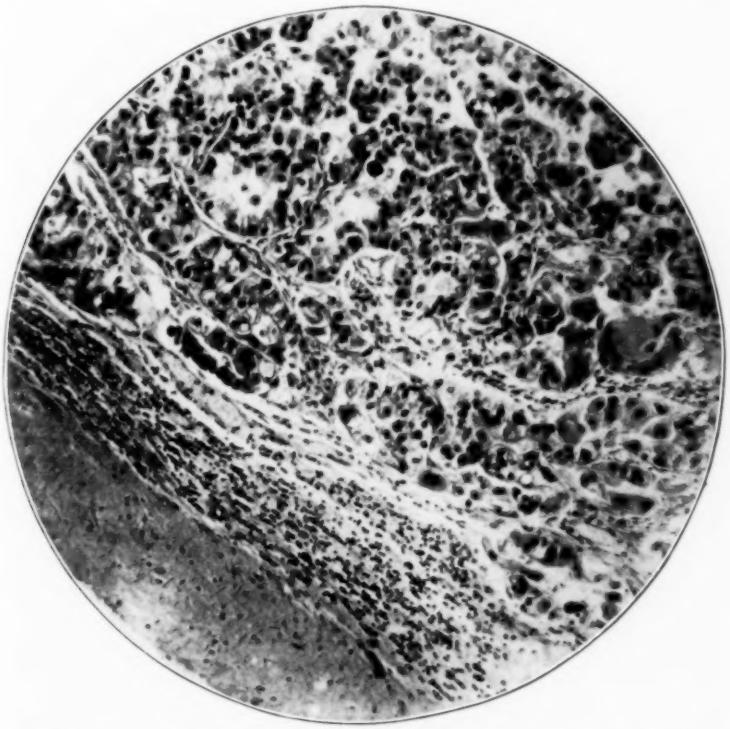

Fig. 4 (Case 6).—Primary carcinoma of the lungs; metastatic tumor in the brain cortex.

that the tip of the lower lobe rested in the left pleural cavity. The upper two-thirds of the upper lobe was composed of a mass of soft material enclosed within a thickened pleura. This portion of the lung was elevated about 4 cm. above the level of the lung, and appeared to be tumor tissue. On cut surface, this area was composed of soft, moderately coherent, whitish material. The center of the mass was necrotic, semifluid, pinkish white and contained small, whitish, gelatinous bits of tissue. The upper part of the lower lobe was firm and light in color. The lower part was deep red and soft. The posterior mediastinum, on dissection, showed several enlarged lymph nodes which on cut surface were pale, soft and fleshy. The other organs showed no pathology in gross.

Microscopic Examination.—Tumor: Sections from the tumor showed polygonal cells with large, clear, round nuclei loosely grouped between narrow branching connective tissue septums. The cells lay either singly or in groups, with distinct spaces between the cell groups, often containing polymorphonuclear leukocytes. In many areas, the tumor cells were in all stages of necrosis. The nuclei were pyknotic and fragmented or absent, and the cell protoplasm stained deep red with eosin. Degenerated polymorphonuclear leukocytes mingled with this material. Mitotic figures were numerous. No cilia were seen in the cells. Lung: Sections of the lung below the tumor area showed the bronchi and alveoli filled with polymorphonuclear cells and fibrin and endothelial cells containing blood pigment. The bronchial walls were necrotic. Lymph node: A section from a mediastinal lymph node showed definite invasion by tumor cells. The spleen and liver showed passive congestion.

The pathologic diagnosis was primary carcinoma of the right lung (bronchial cell origin?) with metastases to mediastinal lymph nodes; organizing pneumonia, chronic fibrous pleurisy; lung abscess, and chronic passive congestion of the liver and spleen.

Histologically, the tumor in this case did not differ from those previously described. It metastasized only to the mediastinal lymph nodes. From the clinical point of view, the history, physical examination and the course of the disease were typical for a lung neoplasm.

CASE 8.—*History.*—W. S., a man, aged 52, was admitted to the Boston Sanatorium, July 8, 1922, with the chief complaint of pain in the back and the left side of the chest, and cough for the last six months. The past and family histories were negative.

Six months before admission (January, 1922), the patient began to have pain in the back and in the left side of the chest, at first sharp, later dull; the pain was intermittent, lasting for about twenty minutes, and was worse on lying down, and was not related to meals or micturition. Two months later, he had a cough productive of a moderate quantity of thin, white, mucoid sputum streaked occasionally with blood. One day in March, according to the patient's statement, he had a hemorrhage, coughing up one third of a glass of bright red blood. Before entering the hospital, the patient went to several clinics, and, in April, 1922, was admitted to the Massachusetts General Hospital. His record while there was as follows:

April 3, the history of hemoptysis seemed definite, and suggested tuberculosis strongly. He had lost little weight, and had few pulmonary symptoms. The right side of the chest showed an increased whispered voice at the apex, but no râles were heard. The sputum had been blood streaked.

April 4, fluoroscopic examination revealed that the upper half of the left chest showed a marked decrease in radiability, apparently with a sharp lower border about the interlobar septum. The trachea and the heart were displaced to the left. The left diaphragm was fixed. The left apex did not light up. The right side showed considerable mottling around the root beneath the clavicle; otherwise, it was clear. The right diaphragm moved normally. The posterior mediastinum was obscured. These changes probably represented an extensive destructive and fibrosing process in the right upper lobe with retraction of the mediastinal contents to the affected side. On the left, the fine mottling suggested small bronchopneumonia areas.

April 5, clinically, the signs suggested fibrosis of the right apex with shrinkage, while the right clavicle was thrown out. There was distortion of the spine, drawing the mediastinum to the right. Syphilis was excluded. There was no evidence of new growth. It was possible that there had been some chronic interlobar infection. The chances were in favor of chronic tuberculosis. The diagnosis was pulmonary tuberculosis (chronic fibroid).

April 9, the patient was discharged to the local physician.

Physical examination, at the Boston Sanatorium, July 8, 1922, showed the patient a well developed but poorly nourished man. The skin was dry, and was not jaundiced. The upper part of the chest in front was covered with tinea versicolor. The heart was negative. In the lungs, the left apex was moderately dull, with a few fine râles; in the right, there was dulness and bronchial breathing from the apex to the inferior angle of the scapula, with increased voice sounds. Below, to the base, there was flatness and a complete

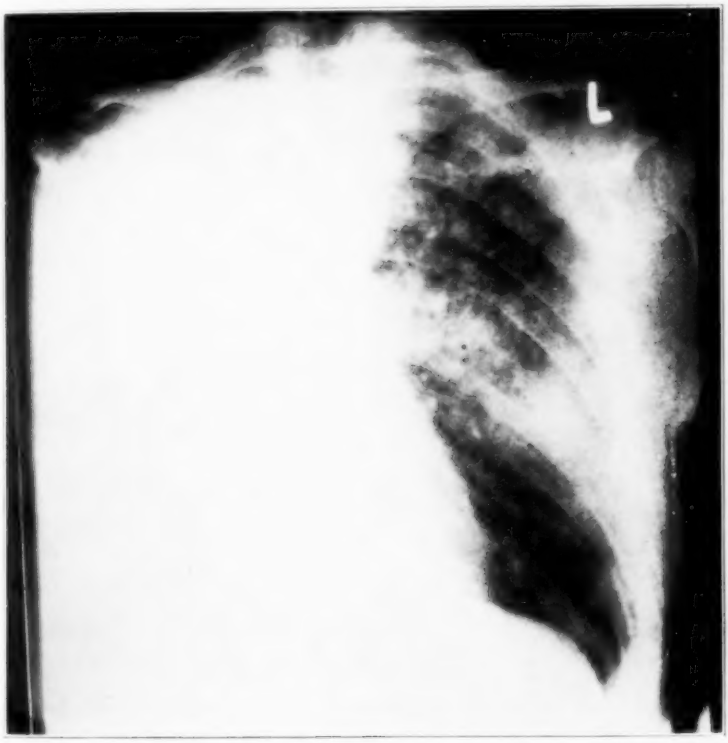

Fig. 5 (Case 8).—Primary carcinoma of the lungs; roentgenogram taken about ten weeks before the patient died.

absence of breath sounds. In the abdomen, the liver was felt 10 cm. below the costal margin with a slightly tender and somewhat nodular edge. The genitalia were negative. The prostate was not enlarged or painful on palpation. In the bones, there was right lumbar scoliosis.

July 12, the patient was tapped, and 900 c.c. of straw colored fluid was withdrawn from the right pleural cavity.

The urine and stools were negative. The sputum was negative on six examinations for tubercle bacilli. The patient died after nine weeks in the hospital.

The clinical diagnosis was pulmonary tuberculosis.

Necropsy.—The necropsy was performed by me, six hours post mortem. The body was that of a well developed and very poorly nourished white man, 162 cm. in length. The skin had a cachectic hue. The upper part of the chest was covered with tinea versicolor. There was a slight scoliosis to the left in the region of the second and third lumbar vertebrae. The legs were slightly edematous. The pericardial cavity and heart were normal.

Lungs: The left lung weighed 1,100 gm. The organ had a normal color and was enlarged, partially covering the heart. On palpation, it had a finely

Fig. 6 (Case 8).—Primary carcinoma of the lungs; anterior aspect of the right lung; *TP*, thickened pleura.

granular feel, as if it were filled with very small glass beads. Between the nodules, the lung was normal, being elastic and crepitant. On section, the cut surface appeared to be peppered with disseminated, grayish nodules, from 2 to 3 mm. in diameter, which gave the lung a coarsely granular feel. The mucosa of the bronchi was congested, but did not show any evidence of invasion by tumor. The vessels were not remarkable on gross examination. The right lung weighed 600 gm. The organ was contracted, and occupied only the upper part of the pleural cavity. On palpation, the lung was firm and had a somewhat beefy feel. The surface of the lung was smooth and glistening. At the apex, the pleura, which was here about 0.5 cm. in thickness, was firmly

adherent to the lung, and the whole lung looked as if it were suspended in the pleural cavity by its apex (Figs. 6 and 7). On section, the lung somewhat resembled a pneumonic lung in the stage of red hepatization. Scattered all over the organ, but most marked at the apex, small grayish white nodules, one-half cm. in diameter, were seen. The bronchi and larger vessels were macroscopically free from any tumor invasion, and, except for a congestion, appeared normal. In some smaller vessels, grayish, pin-point elevations were conspicuous and seemed to be tumor nodules. The bronchial lymph nodes were enlarged and firm. When the left lung was removed, a tumor mass was

Fig. 7 (Case 8).—Primary carcinoma of the lungs; posterior aspect of the right lung; *B*, bronchus; *P*, pericardium.

found in the pleural cavity, measuring 7 by 3 by 2 cm. It had a coarse appearance, and was hard and resistant to the knife. The whole mass was situated under the periosteum of the fourth rib on the left, beginning at the junction of the latter with the vertebral column. Several small nodules of the same character were found on the same rib. The mediastinal lymph nodes were large and firm, due to invasion by tumor. The pleura, on both sides, was thickened and contained tumor nodules. The liver weighed 1,800 gm., and extended 12 cm. below the ensiform process. At the lower margin of the right lobe, a tumor mass, about 6 cm. in diameter, was found. The new growth was grayish white, resembling in color a freshly cut slice of bacon. In the neighborhood of the large tumor mass, and scattered all over the organ, several

small nodules, from 0.5 to 2 cm. in diameter, closely resembling the main tumor, were found. The capsule of the liver did not seem to be thickened. The large veins did not contain any visible tumor masses. The gallbladder was slightly distended with bile, and its mucosa did not contain scars or ulcerations. The ducts were patent. The pancreas weighed 100 gm., and was essentially negative. The kidneys showed passive congestion. The suprarenals, gastrointestinal tract, genitalia and aorta were normal.

Fig. 8 (Case 8).—Primary carcinoma of the lungs; tumor cells replacing the normal alveolar lining; alveoli distended and alveolar walls greatly thickened.

Microscopic Examination.—Lungs: In the right lung, the tumor was made up of epithelial cells which varied in shape from cuboidal to columnar. The cytoplasm of the cells was large and irregular, and their nuclei vesicular, round or somewhat oval, containing from 1 to 2 eccentrically situated nuclei. The tumor was confined exclusively to the alveoli, in which the normal alveolar lining was replaced by tumor cells (Fig. 8). The whole lung showed a very marked sclerosis, due to the deposit of fibrous tissue stroma of the epithelial tumor which had invaded the alveoli, leading to marked thickening of the alveolar wall. Due to this process, there was much hemorrhage, and the alveoli contained hemosiderin. Some alveoli were filled with coagulated serum and débris. Cells, singly and in clumps, with a tendency to form alveoli were found. Scattered over the sections, a lymphocytic infiltration was seen with

patches of necrosis. There was an invasion of the pleura by tumor, the cells of which resembled closely those of the lung and arranged themselves in small acini. The pleura was very much thickened and consisted of dense fibrous tissue. In the left lung, the tumor was scattered throughout the whole section, and the tumor nodules varied in size from individual tumor cells to tumor masses, from 1 to 2 mm. in diameter. The tumor cells here did not differ from those in the right lung by their tinctorial properties, morphologic character or arrangement. In many areas, tumor had broken into the alveoli, replacing their normal lining and producing some fibrosis. Tumor was found in some small vessels and in general was very conspicuous alongside the vessels, probably in the perivascular lymphatics which were markedly dilated. Mitotic figures were quite frequent. In places free from tumor, except for an emphysematous distortion of some alveoli, the lung proper presented a fairly normal appearance. The pleura on this side also was thickened and invaded by tumor cells, arranged in duct-like manner with distended lumina. The remainder of the pleura consisted of dense, fibrous tissue. The vessels in both lungs were engorged with blood. The bronchi and bronchioles showed the epithelial lining partly desquamated in areas. No inflammatory or hyperplastic changes could be found here.

Rib: Here also the tumor had the same alveolar arrangement and the same type of cells. It differed from the growth in the lungs in that the alveoli were in general much larger, somewhat resembling cysts, and the connective tissue stroma was rather abundant.

Liver: The main tumor in the liver was made up on the same type of cuboidal or columnar epithelial cells and also was arranged in acini. The other organs did not show any noteworthy microscopic changes.

The pathologic diagnosis was primary carcinoma of the right lung (probably of alveolar origin) with metastases to the left lung, pleura, rib and liver; hemothorax (right); sclerosis of the right lung; chronic fibrous adhesive pleuritis, and passive congestion of the spleen and kidneys.

The histogenesis of the tumor is of interest. It was judged that the tumor originated in the epithelium lining the alveoli, replacing the normal alveoli lining and leading to a sclerosis of the lung with a marked thickening of the alveolar walls (Fig. 8). The possibility of such an origin has been much discussed and contested by many authors. Ewing,[1] Ménétrier [4] and the greater majority of pathologists, however, include this type of long carcinoma in their classification. The tumor is classified as "of alveolar origin" on the gross and microscopic pictures. Microscopically, no signs of new growth could be detected in the larger or smaller bronchi after a long and careful search. The tumor was not confined particularly to the bronchial submucosa—the usual place of origin of mucous gland cancers. Microscopically, the replacement of the alveolar lining by tumor cells was diffuse throughout the entire organ, instead of having occurred in only a few areas, as is seen occasionally in "bronchial origin" tumors (Fig. 2, Case 4). The gross appearance of the right lung in this case is of interest and is unusual (Figs. 6 and 7). From the clinical point of view, the case is typical, with its gradual onset, course and duration.

Case 9.—*History.*—A. B., a man, aged 64, entered the Peter Bent Brigham Hospital, May 6, 1923, complaining of cough and fever. The family history was not remarkable. Fourteen months before, he had some wheezing and

shortness of breath, lasting for about six months. He entirely recovered from this and was well, until six months before, when he began to have an unproductive but very distressing cough which varied with the weather, being worse during a cool spell and increased by exertion. This had kept up ever since with very little sputum, but, on one occasion, he had hemoptysis. The only pain he had had was substernal and in the epigastrium after paroxysmal coughing. He had lost 10 pounds (4.5 kg.) in the last year. The roentgen-ray

Fig. 9 (Case 9).—Epidermoid carcinoma of bronchus; posterior aspect of both lungs, trachea and main bronchi; tumor in right (wider) bronchus and right lung.

examination, two months previous to his admission to the hospital, showed a rounded shadow just to the right of the heart shadow, suggestive of a mediastinal tumor.

Physical examination showed dulness over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area. The heart was apparently displaced to the right. The temperature was ranging between 99.8 and 103.8 F.

The blood Wassermann reaction was negative. The sputum was mucopurulent and was negative for tubercle bacilli. The stools and the urine were

negative. The hemoglobin was 98 per cent. The red blood cell count was 4,870,000 per cubic millimeter, and the white cell count, 19,000 per cubic millimeter. The differential count was normal. The roentgen-ray examination, on entrance, showed marked clouding of the right base. The heart, trachea and mediastinum were displaced to this side. The "rounded shadow" originally noted was not evident at present, apparently being obscured by the heart shadow.

The patient remained in the hospital twenty-two days, during which time he lost about 10 pounds (4.5 kg.) in weight. Except for signs of a very slight amount of fluid in the right chest, the clinical picture did not change. He was discharged, May 28, unimproved.

Fig. 10 (Case 9).—Epidermoid carcinoma of bronchus, showing tumor nodules covering the exposed heart; *N*, tumor nodule.

The clinical diagnosis was malignant disease of the mediastinum.

June 13, he was readmitted to the hospital. On physical examination, no marked changes were noted. The patient remained in the hospital three days, and was discharged with the diagnosis of carcinoma of the lungs. At home, he developed occasional hemoptysis. The cough and fever continued. He died, April 18, 1924.

The clinical diagnosis was primary carcinoma of the lungs.

Necropsy.— The necropsy was performed by Dr. S. B. Wolbach, fifteen hours post mortem. The body was poorly nourished and did not show any

marks worthy of note. The peritoneal cavity, except for the presence of about 750 c.c. of clear, yellow fluid, was not remarkable. The pericardial cavity was distended with about 150 c.c. of a dark red fluid containing flecks of fibrin. The pericardial surfaces, parietal and visceral, were covered with a red, shaggy, adherent, fibrinous material. The heart was normal in size. The striking feature of the organ, in addition to this fibrinous exudate, was the presence of several, from fifteen to sixteen, elevated nodules, from 4 to 12 mm. in diameter, which were distributed fairly uniformly over the right and left ventricles (Fig. 6). On incision, they were white, fairly firm and regular,

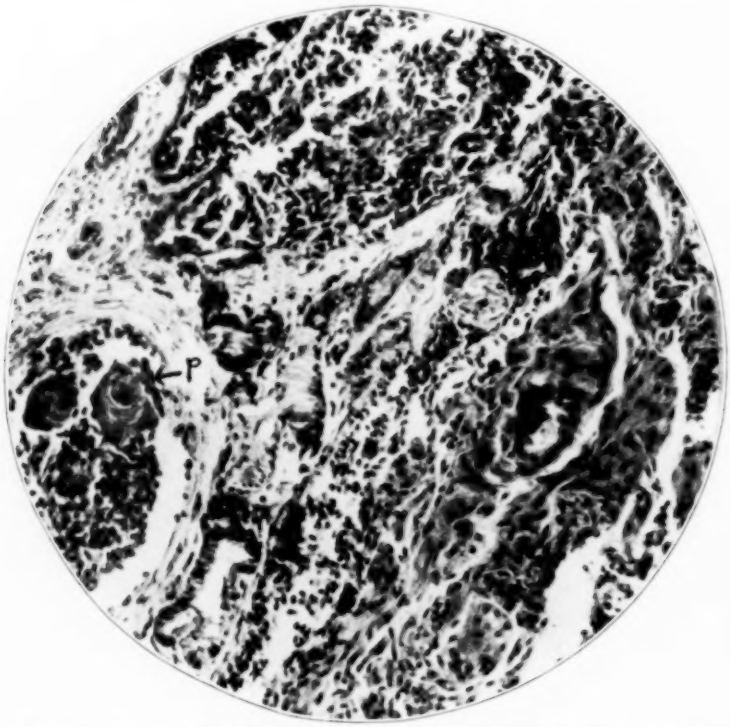

Fig. 11 (Case 9).—Epidermoid carcinoma of bronchus; *P*, pearl formation.

and pressure caused to exude droplets of white material, which subsequent microscopic examination showed to be keratinized and necrotic epithelial cells.

Chest: The ribs and sternum were adherent on the right side to a thickened pleura along the anterior border of the right lung, and to a hard, firm mass overlying the ascending aorta. The tissues at the anterior mediastinum were edematous. The right pleural cavity was entirely obliterated by very dense tissue. The left cavity was free and contained about 1 liter of clear, deep yellow liquid.

Lungs: The right lung was freed by stripping the parietal pleura, and the lungs and heart were removed en masse with the right side of the diaphragm. The pleura over the posterior border of the right lung ranged from 3 mm. to 6 mm. in thickness, and consisted of dense, white, fibrous tissue with firmer

white plaques, from 2 to 4 mm. thick, composed of friable tumor material. There were a few pigmented lymph nodes at the anterior border of the diaphragm which contained numerous white nodules. On opening the trachea and bronchi, the trachea, except for deep injection, was normal. The left primary bronchus also was normal. The right was practically occluded 2 cm. below the bifurcation. Anteriorly, the wall of the right primary bronchus was replaced by a friable, white tumor tissue which, on pressure, exuded soft, white material which, on subsequent examination, proved to contain desquamated epithelial cells, the largest part keratinized (Fig. 11). The only branch of the right primary bronchus that could be found was one leading to the upper part of the right lobe, and the orifice of this bronchus was nearly completely occluded by tumor tissue. Below, the bronchus ended abruptly in a mass of friable tumor, from 1 to 3 cm. in thickness, which extended downward along the inner posterior margin of the lung for a distance of 8 cm. Anteriorly, the tumor, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer, 1 cm. thick, which extended upward over the ascending portion of the arch. Two parallel incisions were made through the posterior borders of the lungs and showed that the whole lung was atelectatic, with here and there small bronchiectatic cavities. The whole of the upper lobe was tough and fibrous in consistency, and in the peripheral portion of the lung were a few nodules, a few centimeters in diameter, of friable tissue. These tumor nodules were most abundant in the lower lobe. The left lung was not incised. On the inner surface of the lower lobe, that is, in contact with the pericardium, there were two plaques of tumor, each a few millimeters thick and 1 cm. in width. The head was not opened. The other organs were normal.

Microscopic Examination.—Lungs: The tumor grew without any definite arrangement. Nests or masses of cells were scattered over the sections surrounded by thick bands of dense fibrous tissue. The tumor cells individually were large, polygonal or elongated and irregular in outline. The cytoplasm was finely granular and stained in blue. The vesicular nucleus occupied the greater part of the cells, was large, rich in chromatin and contained a centrally located, very deeply stained nucleolus. The cells varied slightly in size. Large cells with many nuclei, resembling giant cells, were encountered here and there. In many areas, mostly in the center of the tumor masses, the cells had a tendency to arrange themselves in concentric layers and were conspicuous. Here, the cells were usually larger than the tumor cells; their cytoplasm was stained deep red with eosin, and the nucleus seemed generally to be smaller. These masses of cells had the typical appearance of a cornified epithelium met with in the so-called "pearls" of the epidermoid carcinoma. Here also there was a definite tendency to "pearl" formation (Fig. 11). These keratinized masses were sharply demarcated from the rest of the tumor. Wide areas of necrosis were seen in practically all sections. The lung tissue adjacent to the tumor, but free from the new growth, showed extensive fibrosis, in areas dense and avascular, in areas rather loose and richly supplied with blood. Large endothelial cells loaded with a brown pigment were disseminated occasionally among the tumor cells and, more conspicuously, in the preserved and compressed or distorted alveoli. Anthracosis and round cell infiltration was seen here and there. The pleura showed invasion by tumor which showed the characteristics of the main tumor. The lymphatics were greatly distended by tumor nodules, which occupied the greater part of their lumen.

Esophagus: The tumor here was confined to the muscularis mucosa and submucosa and was identical to the lung tumor. It was sharply demarcated from the normal tissue. The esophageal mucosa was intact. Mitotic figures in the main tumor, as well as in the metastases, were of a rare occurrence. From the gross appearance and histologic examination, it was judged that the tumor was a slowly growing epidermoid carcinoma originating in the mucosa of the right bronchus. The spleen showed amyloid infiltration. The liver

showed passive congestion and slight central necrosis. The kidneys showed slight arteriosclerotic changes. The other organs were normal.

The pathologic diagnosis was epidermoid carcinoma originating in the right primary bronchus with metastases to the pleura, left lung, heart, regional lymph nodes and esophagus; hydrothorax (left); hemopericardium; ascites; amyloid degeneration of the spleen, and passive congestion of the liver.

It will be noted that the tumor in this case was a slowly growing epidermoid carcinoma originating in the right bronchus. Since the bronchi are normally lined with columnar ciliated cells, the squamous type of cells in this kind of tumor is believed to be due to a conversion of the columnar cells. This conversion or metaplasia is defined as "a transformation of one well characterized tissue into another equally well characterized but morphologically and functionally different." This transformation is, however, limited to epithelial tissues only. The intimate mechanism of this conversion is, as yet, under discussion. It is observed, however, that metaplasia of epithelium is always due to a previous long standing chronic irritation, viz., inflammation. A typical example of such a transformation is seen in leukoplakia of the tongue. Richey [16] reported a case of leukoplakia of the pelvis of the kidney due to a chronic colon bacillus inflammation. Wells [17] described a case of a primary squamous cell carcinoma of the kidney, and considered renal calculi which were present in this case to be the direct cause of the metaplasia which ultimately resulted in malignancy. Wells produced evidence to show that "metaplasia involves not only a morphologic but a chemical transformation of the cells." Haythorn [18] observed metaplasia of bronchial epithelium in three cases of unresolved pneumonia.

The tumor in the case reported grew very slowly, the duration of the disease being about sixteen months.

Case 10.—*History.*—J. E. C., a man, aged 38, a gardener, entered the Peter Bent Brigham Hospital, July 2, 1924, with the complaint of progressive weakness and loss of weight. The past and family histories were negative.

The present illness began, eight months before admission, when he noticed that he was getting unusually weak, and at the same time his friends called attention to the fact that he was getting very thin. Within the following two months, he lost 20 pounds (9 kg.), 10 pounds (4.5 kg.) of which he has regained in the last six months, by not working, as he said. His appetite became poor about three weeks before. One week before, he began to swell up in front of the left shoulder. For three or four weeks, he had had a cough, coincident with a cold. The cough was present only in the afternoon, and he raised slight quantities of normal looking sputum. He had become so weak that he could hardly sit up in bed. He had been hoarse for one month. He had noticed clubbing of his fingers, the left hand particularly, in the last two weeks.

Physical examination showed a fairly well developed and very poorly nourished cachectic man. There was an edema involving the left shoulder and apex regions. The expansion of the chest was less marked on the left.

16. Richey, D. G.: J. Lab. & Clin. Med. **5**:635 (July) 1920.
17. Wells, H. G.: Arch. Surg. **15**:356 (Sept.) 1922.
18. Haythorn: J. Med. Res. **21**:593, 1912.

The respiration was 26, and of shallow depth. The thorax was narrow and ptotic. The heart and aorta showed no pathologic condition. The pulse was 110, and was even and regular. The arteries were not remarkable. The veins were dilated in the left arm and neck, and slightly in the right arm. The blood pressure was: systolic 85, diastolic 65.

In the lungs the expansion was diminished on the left side. On palpation, no friction rubs were heard. Vocal fremitus was diminished on the left side

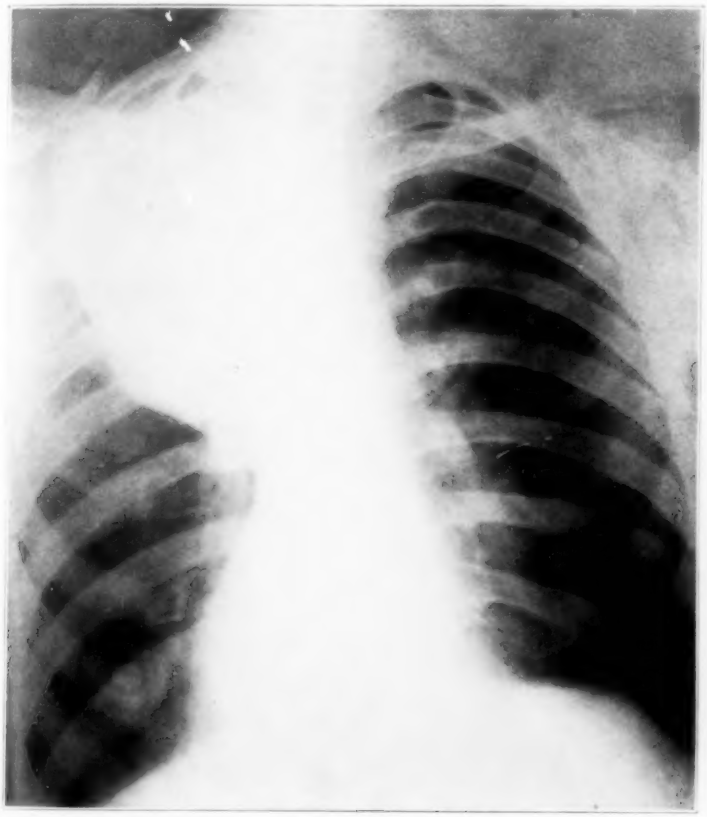

Fig. 12 (Case 10).—Carcinoma of the left lung. (Courtesy of Dr. M. Sosman.)

and practically absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border and to the posterior axillary line. Anteriorly, it was dull at the apex, up to the second interspace; below that, normal for an interspace and then markedly tympanitic up to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed posteriorly diminished bronchial breathing at the apex down to the angle of the scapula. Below that, for a stretch of two or three interspaces, the breath

sounds were purely bronchial and close to the ear; at the base, there was distant bronchial breathing. The whispered voice corresponded. Anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base, there was distant bronchial breathing. The right side did not show any pathologic condition. The voice did not sound abnormal. The rest of the physical examination, except for the clubbed fingers noted, which were more marked on the left, was not remarkable.

Roentgen-ray examination of the chest, June 10, showed (Fig. 12) a large, smooth, dense shadow occupying the upper third of the left lung, extending as low as the eighth rib posteriorly, along the border of the spine and in the third rib in the axillary line. Fluoroscopically, this mass did not pulsate, was not connected with the esophagus, displaced the trachea very slightly and showed no fluid level. The adjacent ribs and spine all appeared normal. The impression of the roentgenologist was that there was a tumor, probably arising in the lung, possibly metastatic.

Reexamination of the chest, July 7, showed a marked generalized haze over the entire left half of the thorax, with a sharp, pleural line along the left axilla, which was characteristic of fluid in the pleural cavity. The heart, aorta and trachea were displaced to the right. Fluoroscopy showed paradoxic movements of the diaphragms, the left rising and the right falling at inspiration. (The latter suggests bronchial obstruction on the left.) The definitely outlined shadow previously seen could not be identified.

The blood Wassermann reaction was negative. The leukocytic count was 16,000 per cubic millimeter; the erythrocytes were 2,800,000 per cubic millimeter.

July 5, the patient was tapped, and 1,200 c.c. of an opalescent fluid was removed, which showed a specific gravity of 1.010 and 100 per cent. mononuclear cells.

July 10, a second thoracentesis was attempted. Fluid could not be obtained. On suction, a few small pieces of necrotic material were obtained, and were sent to the pathologic laboratory. The pathologic diagnosis was carcinoma.

Due to a secondary infection, the patient ran a septic fever. He remained in the hospital twenty-two days and died.

The clinical diagnosis was carcinoma of the left lung.

He had had previous hospital entries at Newton Hospital and at Huntington Memorial, Boston, recently. No diagnoses were made there.

Necropsy.—The necropsy, performed by Dr. H. Pinkerton and myself, showed a very poorly nourished, cachetic, white man, measuring 170 cm. in length. The external examination revealed clubbed fingers, more pronounced on the left; a large decubitus over the sacrum; a slightly prominent abdomen, and a hard, palpable lymph node in the right axilla. Otherwise, the external examination of the body was not remarkable. A primary incision revealed only slight traces of fat over the chest and abdomen. The peritoneal cavity contained 150 c.c. of clear, straw colored fluid. A membranous exudate about 2 mm. in thickness was found overlying the lower portion of the sigmoid colon. Between the hepatic and the splenic flexures, the colon was extremely ptotic, hanging down to the brim of the pelvis. A calcified lymph node 1 cm. in diameter was found in the mesentery of the small intestine, containing some cheesy material.

Pleural Cavities: The right cavity contained about 100 c.c. of a clear yellowish fluid. The cavity was free throughout. Both the parietal and visceral pleurae were smooth and glistening, and showed no inflammatory changes or invasion by tumor. The left cavity contained about 300 c.c. of fluid similar to that found on the right side. The cavity was free, except at the apex and posteriorly, particularly along the spine and posterior chest wall where it was obliterated by extremely strong adhesions. The left lung appeared normal in front and in the axillary region from the beginning of the third rib

downward; posteriorly, only the lower lobe was free from tumor. The visceral pleura in the areas untouched by new growth was normally thin and translucent, and the lung was rather pale and slightly emphysematous. The lungs and heart were separated from the pleural cavity en masse.

Owing to strong adhesions, the apical part of the tumor and that part along the spine were torn on removal, a portion being left in the chest. When the visceral pleura was thus torn, it seemed that the tumor walled off by the pleura shelled out from the latter and appeared twice as large as seen in situ.

Fig. 13 (Case 10).—Epidermoid carcinoma of left lung, showing anterior aspect of both lungs; tumor is seen above the line.

The tumor was grayish white, moderately firm and somewhat friable. It was composed of one large mass and on the surface in front, a couple of nodules, from 3 to 5 cm. in diameter, were seen. The tumor was sharply demarcated from the lung parenchyma.

Trachea and Bronchi: The trachea appeared normal. Its mucosa was pale and covered with a colorless, frothy fluid. The right bronchus and its divisions showed no changes. The main stem of the left bronchus entered as usual the lower lobe of the lung and its dissected ventral and dorsal branches were patent and contained no pathologic condition. The first branch of the left bronchus (normally distributed to the superior lobe) was normal throughout.

Two of its larger intrapulmonary branches, the lower and middle, were patent and appeared normal only for about 3 cm. and were occluded at the end by tumor. The other intrapulmonary branches distributed in the superior part of the upper lobe could not be traced at all, being entirely surrounded by tumor and destroyed.

Lymph Nodes: The tracheal, tracheobronchial and mediastinal lymph nodes were carefully investigated and did not show any invasion by tumor. The nodes below the bifurcation seemed to be enlarged, without, however, any

Fig. 14 (Case 10).—Epidermoid carcinoma of left lung, showing posterior aspect of both lungs; *LB*, left bronchus; *MS*, main stem of left bronchus.

tumor invasion. The third and fourth ribs at the junction of the vertebrae and two thoracic vertebrae were eroded in areas of the tumor attachment, but no invasion of the bone could be demonstrated. The other organs, carefully examined, did not reveal the presence of any new growth or other noteworthy changes.

Microscopic Examination.—Lungs: Sections taken from different parts of the tumor showed the tumor to be composed of polyhedral cells having a large cytoplasm and a voluminous vesicular nucleus. These were arranged in columns and strands from 2 to 3 cells broad, which anastomosed and branched. In

one section, the cells had a somewhat tubular arrangement, showing their nuclei compressed, pushed toward the periphery and having a rosette-like appearance. In another section, the tumor was rather solid, being arranged in small clumps of cells or short rows of single cells. The cells contained a great variety of inclusions, resembling in areas "parasites" described by some writers, and, occasionally, so-called "bird's eye" inclusions. Round globules of a different size stained in black with methylene blue eosin were conspicuous all over the sections. There was no definite keratinization or pearl formation, but only a tendency to this, particularly in the centers of the larger clumps of cells. A great deal of fat was seen in the cells, as well as between the cells. The stroma of the tumor consisted of a loose, edematous connective tissue infiltrated with small round cells, and here and there with single tumor cells. The tumor was sharply demarcated from the lung parenchyma, which showed compression of the alveoli and thickening of the alveolar wall. Mitotic figures were seen rarely. The lymph nodes showed no signs of tumor. The other organs, except for the kidneys which showed an early parenchymatous nephritis, were not remarkable.

The pathologic diagnosis was epidermoid carcinoma of the left lung of bronchial origin; chronic adhesive fibrous pleuritis; hydrothorax (bilateral); peritonitis; decubitus; clubbed finger, and cachexia.

Nine months before death, the patient began to complain of progressive weakness and of loss of weight. These complaints were the leitmotif of the entire clinical history. The duration of the disease was certainly much longer than nine months, and, as in the previous cases, its real onset was impossible to determine. Of a particular interest in this case was the absence of any complaints referable to chest organs: cough, hoarseness and pain in the chest. It will be seen that the symptoms, loss of weight and weakness, were characteristic of malignancy anywhere in the body. On staff rounds, the visiting physician demonstrating the case said, "It is unusual to have a primary growth in the lungs without cough as the most outstanding feature." By analyzing the cases here reported, one will see that cough was present only in Cases 7 and 9, but was not, however, a prominent feature even in these cases. This case, once more, outlines the "clinical polymorphism," so to speak, of primary lung cancer, and the atypical course it usually runs.

The diagnosis, in this case, was made on a rather incidental "biopsy," due to a suggestion from the pathologic department to insert into the chest a larger needle and to try to aspire some tumor material for pathologic diagnosis.

The pleural fluid obtained at necropsy and examined by myself after it had been centrifugalized (a smear stained with methylene blue), in addition to small lymphocytes, showed also epithelial cells of an unmistakably malignant nature. It was remarkable that whereas the lymphocytes, in the smears, were always single, the tumor cells were gathered almost always in clumps of five or seven.

Histopathologically, the tumor, as in Case 9, was classified as a slowly growing epidermoid carcinoma originating in a small branch of the left bronchus. It did not metastasize. This is the second case, in the series of ten reported, diagnosed antemortem.

Summary of Cases

Case	Sex*	Age	First Symptoms	Tuberculosis	Cachexia	Fever	Duration,† Months	Clinical Diagnosis	Pathologic Diagnosis	Type of Tumor	Metastases
1	♂	45	Inability to move right arm, diplopia and pain in left eye	No	Yes	Yes	5	Carcinoma, origin unknown	Primary carcinoma of lungs, left lower lobe	Lobar type, bronchial origin, cuboidal and columnar cells	Bones; liver; suprarenals; lymph nodes; fifth nerve
2	♂	44	Pain in abdomen and chest	No	Yes	No	3	Lymphosarcoma ?	Primary carcinoma of lungs, left lower lobe	Lobar type, bronchial origin, columnar cells	Right lung; pleura; liver; regional lymph nodes
3	♀	57	Lumbar pain	No	No	No	7	No diagnosis made	Primary carcinoma of lungs, left lower lobe	Lobar type, bronchial origin, columnar cells	Brain; bones; pleura; right lung; liver; suprarenals
4	♂	55	Brain symptoms; hallucinations, Bell's palsy, projectile vomiting	No	No	No	5	Alcoholic psychosis ?	Primary carcinoma of lungs, left lower lobe	Nodular type, bronchial origin, columnar cells	Brain; leptomeninges; liver; suprarenals; lymph nodes
5	♂	45	Severe headaches and pain in back	No	Yes	No	?	No diagnosis made	Primary carcinoma of lungs, left upper lobe	Lobar type, bronchial origin, columnar cells	Brain; bronchial lymph nodes
6	♂	37	Sharp pain in right shoulder and right knee	No	Moderate	No	3	Pulmonary tuberculosis	Primary carcinoma of lungs, right upper and lower lobes	Lobar type, bronchial origin, cuboidal, columnar and squamous cells	Brain; bone; pleura; left lung; left kidney
7	♂	?	Pain in chest and cough	No	Moderate	Yes, due to septicemia	7	No diagnosis made	Primary carcinoma of lungs, right upper lobe	Lobar type, bronchial ? origin polygonal cells	Mediastinal lymph nodes
8	♂	52	Pain in chest and back	No	Yes	No	12	Pulmonary tuberculosis	Primary carcinoma of right lung	Infiltrating type, alevolar origin, cuboidal and columnar cells	Bones; pleura; left lung; liver
9	♂	64	Cough and fever	No	Yes	Yes	16	Primary carcinoma of the lungs	Epidermoid carcinoma of the right bronchus	Infiltrating type, bronchial origin, squamous epithelial cells	Heart; pleura; left lung; esophagus; regional lymph nodes
10	♂	38	Loss of weight and weakness	No	Yes	Yes, due to peritonitis	9	Carcinoma of left lung	Epidermoid carcinoma of left lung, left upper lobe	Lobar type, squamous epithelial cells	No

* In this table, ♂ indicates male, ♀ female
† Since the onset of the first symptoms.

COMMENT

1. *Metastases.*—The occurrence of metastases in primary lung carcinoma was reported by many observers. In 374 cases reported by Adler, 280 gave metastases. In order of frequency, the regional lymph nodes, liver, pleura and lungs occupy first place, while the brain and bones are very much less frequent.

It will be seen from the accompanying table that in all but four of the cases reported here, there were metastases to the brain and bones. In one instance (Case 1), the tumor involved the medullary portion of the vertebra without producing any changes in the outline of the bone. Such an incidence demonstrates the ease with which bone metastases can be overlooked. In two instances, the brain and the bones were involved; in one, the bones and the fifth nerve, and, in another, the brain and leptomeninges. The invasion of a nerve was reported by Kretchmer and also by Scott and Forman[19] (the tenth). Passler, quoted by Scott and Forman, described extensions of the tumor into the "larger nerves." The appearance of the metastases is apparently early and, as we shall see later, they mask the whole clinical picture.

The analysis of the cases shows that, in Case 1, the first symptoms were directed toward the nerve and bone. In Case 2 the chief complaint was abdominal pain, due apparently to the liver metastases; in Case 3, it was lumbar pain, due to invasion of the lumbar vertebrae. In Case 4, the brain symptoms were the sole complaint. In Case 5, the chief complaint was severe headaches and pain in the back, due to brain and bone metastases. In Case 6, pain in the knee was due to metastasis. Case 7 gave metastases only to the regional lymph nodes. In Case 8, in addition to the characteristic pain in the chest, there was a sharp pain in the back (spinal metastases) which occurred about ten months before death.

The importance of such facts is evident in relation to recent progress in intrathoracic surgery.[20]

2. *Clinical Classification.*—Clinically, primary carcinoma of the lungs is classified in two varieties (Adler, Osler): (1) an acute galloping pleuropulmonic form which runs a very rapid course, from six to twelve weeks; an example of this type of tumor was recently reported by Bergmark and Quensel;[21] (2) a chronic pleuropulmonary carcinoma which includes the bronchopulmonary type, the mediastinal type and the pleuritic type.

As it was pointed out, the tumor possesses not only a vigorous metastatic power, but its metastasis is very early and most of the symptoms are due to metastatic involvement.

19. Scott, E., and Forman, J.: Med. Rec. **90**:452 (Sept. 9) 1916.
20. Lilienthal, H.: Malignant Tumor of the Lung: Necessity for Early Operation, Arch. Surg. **8**:308 (Jan.) 1924.
21. Bergmark and Quensel, F.: Acta med. Scandinav. **59**:710, 1923.

Because of this property, the clinical picture may be divided into two groups: typical—with the chief complaint concerning the chest organs, and atypical—with symptoms due to metastatic involvement.

The difficulties in the diagnosis of the atypical cases, and they are apparently commonest, are often insurmountable. Only the skill of the clinician and some unexpected "accident" lead to a correct diagnosis in such cases. Ameuille [22] reported a case of primary lung cancer recently which gave a typical clinical picture of lung abscess. The roentgen-ray examination was not confirmatory. At operation, pus was found in the thoracic cavity and the French clinician simply, as he says, made a smear from the pus "par curiosité" which, however, revealed that he was dealing with a carcinoma. He labeled his case as a "cancer pulmonaire à forme d' absès." Of twenty-nine cases reported by Cottin, Cramer and Saloz,[5] a correct diagnosis was made in only 20 per cent. Of eight cases, Cramer and Saloz made a correct diagnosis in six instances, or in 75 per cent. The authors add that the encouraging diminution in error "s'explique dans la plupart des cas par de petits accidents accessoires qui nous out mis sur la voie du diagnostic."

As regards the typical cases (in our series, Cases 7, 8 and 9) the diagnosis can usually be made. The onset is, as a rule, gradual. On physical examination in early, and not infrequently in advanced, cases, the auscultatory signs are scant and not characteristic. This holds true in primary as well as in secondary lung cancers.

A cough productive of a mucus or mucopurulent sputum intimately mixed or only streaked with blood is one of the earliest complaints that usually lead to a diagnosis of tuberculosis. Hemoptysis, which is not rare at the onset of the disease, strengthens the diagnosis of phthysis.

Pleurisy with a serous, purulent, or, more often, bloody exudate is not infrequent, but, as is known, it is not pathognomonic of lung malignancy.

A sharp, stabbing pain in the chest, due to an early involvement of the pleura is one of the most characteristic signs of carcinoma of the lungs. There is a complete agreement between the writers on the subject (Wolf, Adler, Cottin, Cramer and Saloz, and Fishberg) that pain in the chest is a very early and constant sign in primary pulmonary cancer. No other disease, and especially tuberculosis, will give such a persistent pain with failure to respond to treatment.

In Cases 7, 8 and 9 here reported, which are apparently more or less typical from the clinical point of view, pain in the chest was the earliest sign and the chief complaint of the patient.

Cachexia is practically always present in cases running a typical course.

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22. Ameuille, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1312 (July 27) 1923.

Fever and night sweats also are occasionally present in lung malignancy.

In cases in which the lesion is confined to the bronchial mucosa or submucosa, respiratory trouble will early point toward a new growth.

The duration of the disease (in typical cases) is practically the same as in carcinoma anywhere in the body. Rapid death (in from two to three months) is reported in some cases. In the cases reported here, the duration (since the onset of the first symptoms) varied from three months to about sixteen months.

Primary carcinoma of the lungs is more than twice as common in men as in women. More than 70 per cent., according to Adler, occurred in men.

The right side is by far the more often affected.

3. *Laboratory Examination.*—A repeated negative sputum for tubercle bacilli, in the presence of perisistent lung symptoms (cough, pain in the chest and blood streaked sputum), especially when in addition there has been a gradually downward course, always suggests malignancy.

Lenhartz [23] found in the sputum of 90 per cent. of cases studied by him, large, spherical cells filled with a multitude of fatty granules and associated with an abundance of epithelial cells that were "strangely deformed" and possessed clublike or taillike projections. He believes that the fatty granules are pathognomonic of pulmonary carcinoma. Osler [24] describes the same cells as a sign of pulmonary cancer, and Adler [2] considers them as "strictly pathognomonic of carcinoma of the lungs."

The presence of tumor cells in the sputum has to be accepted with great caution, taking into consideration the abundance of epithelial cells in a normal expectoration. However, repeated morphologic examination of the fresh sputum cannot be overemphasized.

The exudate is, in the majority of cases, bloody. It contains not infrequently tumor cells and the importance of a histologic examination of the effusion is outlined by all writers. Here, the fixation of the material will furnish more constant and reliable results. The fluid is centrifugalized, and the sediment is fixed in 10 per cent. formaldehyd or Zenker's fluid and run through paraffin.

Bard,[25] by studying the hemorrhagic exudate (pleural, peritoneal) of inflammatory origin and following malignancy, was able to ascertain that, by centrifugalizing the inflammatory exudate (tuberculosis), the supernatant fluid is clear and, on chemical examination (guaiac

23. Lenhartz: XXXVI. Congrès de la Soc. Allem. de Chir., 1907; abstr., Presse méd. **15**:229, 1907.
24. Osler: The Principles and Practice of Medicine, 1919, p. 653.
25. Bard: Compt. rend. Soc. de biol. **103**:170, 1901.

method), contains no traces of blood, while in malignancy (primary and metastatic carcinoma of the lungs, metastatic carcinoma in the peritoneum), the supernatant fluid shows hemolysis. As a result, Bard concluded that the pleural and peritoneal exudate of a cancerous origin possesses a hemolytic action on the patient's red cells, a phenomenon missing in the exudates of infectious origin. Cottin, Cramer and Saloz [5] attribute "an undeniable value to the hemolytic nature of the cancerous exudate." This, however, is not always true. In tuberculous pleurisy of old standing, the supernating fluid does not show hemolysis. Some French writers believe that an exudate rich in albumin (about 40 gm. per liter) may be considered as pathognomonic of cancer.

4. *Roentgen-Ray Examination.*—According to the literature, the roentgenogram in malignancy of the lungs is typical at the onset of the disease. In a study of the roentgenogram in new growths of the lungs, McMahon and Carman [26] arrive at the following conclusions:

1. The roentgen-ray examination and the stereoscopic study of the roentgenograms will early point to a pulmonary lesion and its probable nature.

2. The areas of increased density found in primary pulmonary carcinoma are usually quite typical, and can be differentiated from areas of increased density caused by other diseases in the thorax.

In a recent report, Thomas and Farmer [27] affirm that, by a roentgenogram, the nature of the new growth may be diagnosed before the appearance of clinical signs.

CONCLUSIONS

Primary carcinoma of the lungs is apparently much more frequent than is commonly believed.

Because of the similarity, from the clinical point of view, of primary lung cancer and a great many chronic lung affections, and particularly chronic pulmonary tuberculosis, primary malignancy of the lungs is often mistaken for phthisis or other lung disease.

Primary carcinoma of the lungs possesses a vigorous metastatic power.

From the cases here reported, it seems that the tumor metastasizes very early, and the bones and brain are apparently much more frequently involved than is generally recognized.

The bones may be infiltrated with tumor without producing any change in the outward structure (Case 1).

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26. McMahon, F. B., and Carman, R. D.: Am. J. M. Sc. **155**:34 (Jan.) 1918.
27. Thomas, G. F., and Farmer, H. L.: Am. J. Roentgenol. **11**:391 (May) 1924.

Because of this property (early metastasis), the chief symptom of the patient, as well as the attention of the clinician, is concerned with the secondary involvement, while the primary lesion is often overlooked.

In any case of chronic lung affection with an atypical course and persistence of symptoms, especially if tuberculosis is excluded, malignancy should always be considered. The presence of pulmonary tuberculosis does not exclude the coexistence of malignancy in the same organ.

INTERMITTENT (IMPURE) AURICULAR FLUTTER, WITH SPECIAL REFERENCE TO ONSETS AND OFFSETS OF PAROXYSMS AND THE EFFECTS OF VAGUS STIMULATION *

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The two cases that are the basis for this report exhibited numerous fleeting paroxysms of abnormal auricular action closely resembling auricular flutter. The mechanisms of these paroxysms, as will be pointed out, may be regarded as forms of slightly "impure" flutter. The remarkable never failing brevity of paroxysms, their rapid and at times almost regular recurrence, furnished striking clinical pictures which, as it seemed to us, deserve emphasis as a clinical entity. Furthermore, these cases are of interest since numerous onsets and offsets of clinical circus movement, of which hitherto there have been but few recorded, were obtained. It has therefore been possible to make certain new observations regarding the onset and offset of clinical circus movement and the effects of vagus stimulation and certain drugs on its incidence and duration.

REPORT OF CASES

CASE 1.—J. S., a Polish coal miner, aged 50, was admitted to the Medical Division of the University Hospital, June 27, 1923, complaining of cough and palpitation of the heart. Four months previously he had been almost suffocated by dust during an accident in the mines. Since then he had suffered from cough, palpitation of the heart and shortness of breath so that he had been unable to work. His physician informed him that his heart action was irregular. The patient stated that his abdomen had been swollen for two months before admission, but recently had returned to normal size.

The past medical history was negative except for a mild attack of rheumatism lasting for one month, six years prior to admission. The family history was unimportant, and the social history negative except for the fact that he had been a coal miner for twenty-two years.

Physical Examination.—The patient was a robust, well muscled man, younger in appearance than his stated age. There were no visible evidences of distress or discomfort. There was marked pulmonary emphysema. The heart was enlarged, the transverse measurement being 15.5 cm., and there was a blowing systolic murmur at the apex. The ventricular rhythm was irregularly irregular and the rate ranged from about 80 to 100. The arrhythmia was not abolished by mild exercise. There were no evidences of passive congestion.

Routine examinations of the blood and urine, the Wassermann test and chemical studies of the blood all were negative.

Electrocardiograms.—In Figures 1, 2 and 4, are shown the typical disturbances of cardiac mechanism. There were numerous premature auricular beats, a

* From the Medical Division, University Hospital, and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.

few of which were isolated, but most were followed by short after effects consisting of one or more cycles of abnormal auricular action. In the longer paroxysms there were usually from 6 to 8 cycles. Of these, the first was invariably the longest. A fairly high degree of regularity usually began with either the second or third cycle. In numerous short paroxysms consisting of only three or four cycles, regular action was not established.

Most of the disturbances of rhythm recorded were clearly initiated by premature auricular beats. These occurred apparently haphazard throughout a wide range of auricular diastole. Their effectiveness in initiating after effects did not appear to bear any relation to the degree of prematurity. In a few instances, although details of the beginnings of paroxysms were somewhat obscured by ventricular complexes, the evidence appeared to indicate that paroxysms were initiated by auricular beats of sinus origin (footnote).

There were marked differences in rate of auricular beating during paroxysms, manifesting itself in neighboring paroxysms as well as in those more distant from each other. The lengths of initial cycles (from peak of first

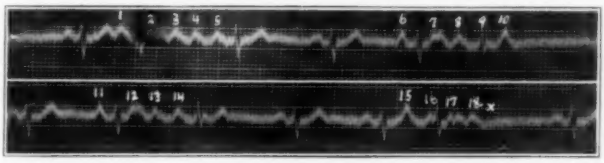

Fig. 1 (Case 1).—Continuous tracing, Lead II. Four short paroxysms, all initiated by premature beats in various stages of auricular diastole. One offset (*x*) is recorded during ventricular diastole.

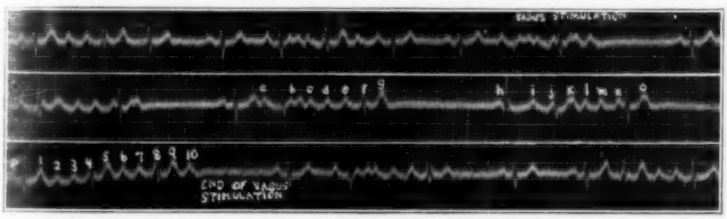

Fig. 2 (Case 1).—Continuous tracing, Lead II, showing effect of vagus stimulation (pressure over both carotid sheaths). The paroxysm from 1 to 10 is longer than any obtained except under vagus stimulation. The cycle *n* to *o* exhibits the exaggerated slowing of rate just preceding offset, sometimes found during vagus stimulation.

deflection to peak of second) varied at least 0.09 second, the extreme measurements being 0.23 and 0.32 second. After regularity was established, the rate of beating ranged approximately from 270 to 360 per minute.

The offsets were usually preceded by the lengthening of the last one and occasionally the last two cycles. In a few paroxysms, offset was abrupt, not being preceded by slowing. After offsets, the duration of periods of auricular inactivity before resumption of normal beating was somewhat variable. Usually, but not always, they exceeded slightly the following cycles of sinus rhythm (postundulatory pause).

The ventricular rhythm was made highly irregular by the auricular action. The initial premature auricular beats were usually followed by ventricular

contractions, but thereafter ventricular response was irregular, occurring after two, three or four of the abnormal rapid auricular beats. Isolated premature contractions and postundulatory pauses also contributed to the irregularity.

Vagus Stimulation.—Results of vagus stimulation are seen in Figures 2 and 3. No influence in the direction of inhibiting onset of flutter was observed after ocular pressure or pressure over one or both vagi. There was a distinct tendency toward slight prolongation of paroxysms during the various types of vagus stimulation. There was also, in some instances, exaggeration of the slowing of auricular beating just preceding offset. One decidedly prolonged paroxysm was recorded in which there was alternate waxing and waning of the auricular rate (Fig. 3, strip 2).

Exercise.—Observations on the effect of exercise were unsatisfactory because the patient did not cooperate well. Mild exercises such as walking up and down stairs rapidly had no manifest effect on the arrhythmia.

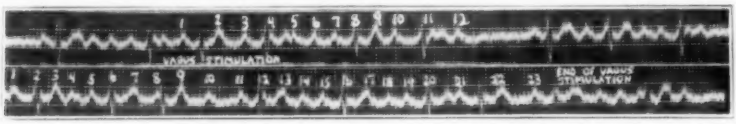

Fig. 3 (Case 1).—Upper strip, Lead II, beginning of a period of ocular pressure. Prolonged paroxysm, with marked exaggeration of slowing preceding offset (9, 10, 11, 12). Lower strip, Lead II, end of a period of ocular pressure. The final portion of a prolonged paroxysm shows definite waxing and waning of rate with marked slowing at 9, 10, 11 and 20, 21, 22, 23.

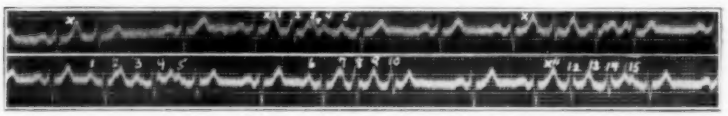

Fig. 4 (Case 1).—Upper strip, Lead II, made just before administration of atropin; lower strip, Lead II, thirty minutes after hypodermic injection of 4 mg. of atropin sulphate. In places (*x*), premature auricular beats appear to bear a constant relationship to preceding beats of sinus origin, suggesting that the premature beats are "re-entrant" and that paroxysms following these events are really initiated by sinus beats. A comparison of initial cycle lengths in second and third paroxysms, lower strip, supports this view.

Atropin.—The effects of hypodermic injection of 2 and 4 mg. of atropin were observed. In both instances, the results were identical. Auriculoventricular conduction during paroxysms was improved so that the rhythm was predominantly two to one (Fig. 4). The incidence of paroxysms was slightly increased. No definite influence was noted in respect of the lengths of paroxysms nor the rates of beating during paroxysms.

Quinidin.—Quinidin sulphate in small doses had no effect on the arrhythmia, but 0.6 gm. three times a day almost completely suppressed it. The cardiac action became entirely regular except for isolated premature auricular beats and occasional abortive after effects consisting of only one or two beats. Quinidin was not well tolerated by the patient and he complained of vertigo and extreme weakness. After discontinuance of the treatment, the characteristic arrhythmia returned within forty-eight hours.

Digitalis.—During the first trial of digitalis, the heart action became entirely regular after digitan in dosage of 0.1 gm. three times a day had been received

for three days. On subsequent trial of the drug, the arrhythmia was again abolished except for occasional isolated premature auricular contractions. Daily small doses of digitalis were continued for ten days and the flutter did not recur. The patient then left the hospital, stating that he felt greatly improved.

CASE 2.—Mrs. T., aged 48, a patient of Drs. Joseph Sailer and Charles H. Frazier, was admitted to Dr. Frazier's service in the University Hospital, Dec. 19, 1923, to be operated on for hyperthyroidism. The heart action was rapid and highly irregular, and could not be differentiated clinically from auricular fibrillation. An electrocardiogram showed numerous premature auricular beats and a few short paroxysms of very rapid auricular action (Fig. 5) which resembled somewhat the paroxysms recorded in Case 1. None

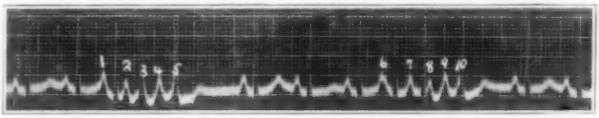

Fig. 5 (Case 2).—Typical brief paroxysms, initiated by premature auricular beats, and showing continuous acceleration up to the abrupt offsets.

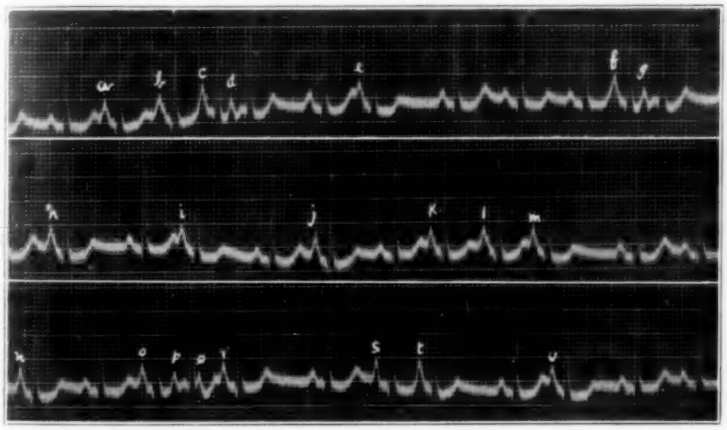

Fig. 6 (Case 2).—Continuous strip, Lead II. Frequent isolated premature auricular contractions. Succession of three premature contractions (*k*, *l*, *m*). Note similarity of deflections, *c*, *d*, occurring after two successive premature beats, to *f*, *g*, which are isolated, and to *o*, *p*, which initiate a very brief paroxysm.

of the paroxysms contained more than five cycles. All were initiated by premature auricular beats of the same form as the isolated premature beats. A regular rate of beating was not established. There was continuous acceleration from cycle to cycle up to point of offset. The cycle intervals of one paroxysm, as measured without special apparatus, were 0.27, 0.20, 0.16 and 0.14 second respectively. The offsets were abrupt.

Following the administration of digitalis, the cardiac rate diminished, the arrhythmia decreased but did not entirely disappear. Bipolar ligation of the

thyroid arteries, one week after admission, was well borne, but the cardiac rate again greatly accelerated and the arrhythmia increased so that it once more simulated auricular fibrillation. A tracing made ten days after operation (Fig. 6) showed isolated premature auricular contractions, successions of premature contractions and short paroxysms of rapid auricular beating similar to those found before operation.

The results of operation were excellent and the patient left the hospital greatly improved. The disturbances of rhythm were greatly diminished and in the course of several months disappeared entirely. The patient was readmitted to the hospital May 10, 1924, and partial thyroidectomy performed May 16. Before operation the heart action was perfectly regular. During the first two days after operation there were numerous premature contractions, and on the third day an arrhythmia that clinically seemed identical with that noted on previous admission. No tracing was made. By the fifth day, the action was regular and has remained so since.

COMMENT

Literature.—Tracings of very brief paroxysms of flutter, onsets and offsets of paroxysms are exceedingly rare. Ritchie [1] in 1912 described and published tracings of an arrhythmia that he designated "an intermittent form of auricular flutter." In Ritchie's case, the arrhythmia continued for a number of weeks. The curves showed short paroxysms of rapid auricular beating separated from each other by periods of auricular inactivity of about 0.7 second duration. There was no normal type of beating separating paroxysms as in our cases. Ritchie states that the auricular deflections during paroxysms were similar to those obtained when the heart was beating normally. In view of this statement, it would appear to be difficult to rule out paroxysmal tachycardia arising in the sinus node or its neighborhood as a possible interpretation of the curves.

Semerau,[2] in 1918, published, along with some tracings exhibiting short paroxysms of auricular fibrillation, one tracing in which a very brief paroxysm was interpreted as auricular flutter. The curves showed some irregularities in the rhythm and the shape of the deflections.

Straus and Hamburger,[3] in a recent report in which the relations between gallbladder disease and cardiac arrhythmias were discussed, published tracings of one case in which short paroxysms of flutter are recorded.

Nomenclature.—According to present day nomenclature, pure auricular flutter is understood to be a condition in which there is established a continuous, rapid, highly regular circulation of the crest of the excitation wave through a fixed path in auricular muscle, and in addition, an orderly spread of the centrifugal waves throughout the auricles. In

1. Ritchie, W. T.: Auricular Flutter, Edinburgh M. J. **9**:485, 1912.
2. Semerau, M.: Ueber Rückbildund der Arythmia Perpetua, Deutsch. Arch. f. klin. Med. **126**:161 (May) 1918.
3. Straus, D. C., and Hamburger, W. W.: The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholelithiasis, Cholecystitis and Duodenal Ulcer, J. A. M. A. **82**:706 (March 1) 1924.

neither of our cases did any of the paroxysms recorded conform strictly to such a standard. They were more comparable to the short "after effects" so frequently observed in dogs following a high rate of stimulation of auricular muscle.

We have naturally hesitated to class these very fleeting disturbances of auricular mechanism observed in our cases under auricular flutter, yet it seemed proper to do so. In Case 1, the auricular deflections were strikingly similar in shape, and irregularity was associated only with onsets and offsets. When the paroxysms lasted long enough, regularity was established. In Case 2, obviously, pure flutter did not occur, yet the similarity in details of the paroxysms to each other (particularly in respect of the shape of the auricular deflections and the progressive acceleration of beating) shows clearly that these disturbances have far more in common with auricular flutter than with auricular fibrillation.

Lewis [4] has described and discussed in detail various conditions found experimentally, which he calls "impure flutter." The disturbances may be very slight and limited to so small a portion of the spread of the centrifugal waves throughout the auricular muscle that they may even escape detection in the axial electrocardiogram. On the other hand, they may be profound and interfere markedly with the orderly course of the central or mother wave. Various gradations between pure flutter and fibrillation have been recorded. Garrey [5] states that impure flutter is essentially the same as pure flutter and should be treated as such, yet it seems to us that the distinctions made by Lewis deserve emphasis, since they afford a basis for a clearer understanding of the mechanisms underlying these conditions. Our cases, as judged from the electrocardiograms, may therefore be regarded as exhibiting impure flutter, not so very far removed from pure flutter, although, as we shall point out, there are doubtless disturbances in the central paths of the excitation waves.

We have borrowed Ritchie's term "intermittent auricular flutter" to direct attention to the intermittent distribution of the paroxysms (particularly well manifested in Case 1).

Onsets.—Lewis, Drury and Bulger [6] state that in the experimental production of flutter "the circus movement which underlies flutter is provoked when an effective shock enters auricular muscle while the latter is in a critical condition. The critical condition is the condition of partial refractoriness brought about by a high rate of beating."

4. Lewis, T.: Observations upon Flutter and Fibrillation, Part IV. Impure Flutter; Theory of Circus Movement, Heart **7**:191 (Aug. 27) 1920.

5. Garrey, W. E.: Auricular Fibrillation, Physiol. Rev. **4**:215 (April) 1924.

6. Lewis, T.; Drury, A. N., and Bulger, H. A.: Observations upon Flutter and Fibrillation. Part IV. The Refractory Period and the Rate of Propagation in the Auricle: Their Relation to Block in the Auricular Walls and to Auricular Flutter, etc., Heart **8**:141 (May) 1921.

Lewis admits, however, that he is not prepared to explain flutter following a single stimulus or breaking in spontaneously on a slow heart rhythm.

De Boer [7] found that single stimuli applied to a frog ventricle some time after recovery from the refractory period caused extrasystole, whereas a stimulus applied immediately after the refractory phase caused a continuous circulation throughout the ventricle. He believed that the weak contraction was followed by a short refractory phase which permitted the circulation of the wave to become established. This hypothesis assumes the temporary presence of localized block (barriers of refractory tissue) in the muscle, initially barring the passage of the wave in certain directions.

Garrey,[5] to whose fundamental work on this subject we owe so much, states that the normal impulse from the sinus region or any other impulse may cause fibrillation and the wildest incoordination of shuttling impulses, if only the musculature is in what may provisionally be called the fibrillary state.

When we come to examine the hitherto scanty clinical evidence bearing on the manner of origin of the circus movement, we find that nearly all the onsets of flutter and fibrillation recorded have taken their origin from ectopic auricular beats. An exception appears to be found in a case published by Semerau,[2] in which curves indicate that two onsets of auricular fibrillation originated from sinus beats.

Our cases show definitely the importance ectopic impulses may assume in the production of clinical circus movement, since out of many hundreds of paroxysms recorded, all in Case 2 and the great majority in Case 1 were clearly initiated by premature ectopic auricular beats.[8] In view of the fact that ectopic beats in our Case 1 falling late in diastole were quite as effective in initiating circus movement as those occurring early, the hypotheses of Lewis and De Boer, which were not meant to apply beyond the experimental conditions presented, cannot

7. De Boer, S.: Eine neue Theorie ueber das Entstehen von Kammerwühlen, Arch. f. d. ges. Physiol. **178**:1, 1920.

8. There is some evidence suggesting that in a few instances among the tracings made in Case 1, auricular beats of sinus origin played some part in the initiation of paroxysms. At times, isolated, highly premature auricular beats occurred simultaneously with T-waves. Their relations to preceding P-waves could not be measured accurately, but in view of their superimposition on T-waves, were undoubtedly fairly constant, suggesting that "coupling" was present. Occasionally this appearance of coupling was followed by a short run of flutter (Fig. 4, upper strip). Under such circumstances, the cycle length from peak of premature beat to peak of next deflection did not show the prolongation present in the first cycles of other paroxysms. The time intervals between the coupled beats did correspond roughly to the time of prolonged initial cycles in other paroxysms. It may be that the highly premature beats were "re-entrant" and their mechanism of the nature of circus movement. Under such circumstances, it might properly be held that paroxysms following these events were initiated by sinus beats.

be valid for Case 1, unless it is assumed that a condition of partial refractoriness of human auricular muscle may persist as long as one second (since during periods of slow rhythm, some of the ectopic beats initiating flutter were approximately that far removed from the preceding sinus beat). Such long periods are apparently possible in the case of junctional tissues, but as to whether or not they may occur in auricular muscle, we have no information. In the present state of our knowledge, we cannot go beyond the statement that some localized block must occur in auricular muscle, preventing the orderly spread of the impulse and thus preserving tissue to become receptive to the wave after it has encircled the chamber traveling in the opposite direction.

The close clinical relationship among premature auricular beats, paroxysmal auricular tachycardia, auricular flutter and auricular fibrillation, has long been observed and commented on. The tracings of our Case 2, we believe, demonstrate particularly well the close relationship among the first three. We find, in a relatively short strip of tracing (Fig. 6), isolated premature beats, successions of premature beats resembling the onsets of paroxysmal tachycardia, a short run of flutter initiated by a premature beat, and two deflections resembling the onset of flutter following two successive premature beats.

It is of interest to note the significance of premature auricular contractions in relation to the circus movement. Our cases show clearly that these may be portals of entry for the circus movement. It is doubtless possible, as observations of Garrey and of Semerau indicate, and as is suggested by some of our curves, that the circus movement may take its origin from a sinus beat. Nevertheless, the statement appears to be justified that if auricular muscle is in a state receptive of the circus movement, premature ectopic auricular contractions favor the entrance of the circus movement far more readily than normal type of auricular beats.

Acceleration of Rate Following Onsets of Paroxysms.—An acceleration of rate was found in the beginnings of paroxysms similar to that found by Lewis, Feil and Stroud[9] in experimentally produced short after effects and flutter. These authors explain this phenomenon as being due to the straining of conduction during the period the stimulation just preceding the circus movement. Consequently the first circus movement of the after effect takes place comparatively slowly, this first slow circuit inducing some recovery of conduction so that the succeeding circuits are accomplished more quickly. In our cases, there is naturally no period of stimulation preceding the circus movement which may be invoked to account for a strain on conduction. If we accept the view

9. Lewis, T.; Feil, H. S., and Stroud, W. D.: Observations upon Flutter and Fibrillation. Part III. Some Effects of Rhythmic Stimulation of the Auricle, Heart **7**:247 (Aug.) 1920.

that conduction is initially retarded, we are unable to relate it to preceding events but must regard it as due to a pathologic state of the muscle.

While we are in no position to deny that change in rate of propagation of the impulse, due either to change in rate of fiber conduction or in the duration of the refractory phase of auricular muscle, may play a part in the acceleration of rate observed in our cases, yet it seems to us that there is another factor to be taken into account that may be of importance. It is unlikely that the foci, from which the initial ectopic impulses spring, lie directly in the path which will be assumed by the crest of the wave after circus movement is established. Consequently, acceleration might be due merely to shortening of the central path during the first few beats, irrespective of any changes in conduction or refractory period.

Offsets.—In view of the fact that in both of our cases the circus movement could not be maintained for more than a few beats (in contrast to nearly all cases of clinical auricular flutter hitherto described), it is of interest to examine the curves of offset. There was one distinct difference between the two cases in the behavior of the circus movement just preceding offset. In Case 1, offset was either abrupt without preliminary disturbance in rate, or more commonly was preceded by distinct slowing for one or two cycles. In Case 2, there was continuous acceleration up to point of abrupt offset. It would therefore appear that the factors concerned in the termination of the arrhythmia were not identical in the two cases.

In the present stage of our knowledge, it must be recognized that attempts to explain the mechanism of offset of clinical flutter from electrocardiograms must be purely speculative. We have no information as to the rate of fiber conduction, the duration of the refractory phase, the position of the central path or possible changes in the central path of the excitation wave. It should be pointed out, however, that in very brief paroxysms, as opposed to established flutter, it is not necessary to assume changes either in the rate of fiber conduction or duration of the refractory period to account for the termination of the circus movement.

In Case 2, the closure of the gap and the termination of the circus movement may have been brought about by the election of a progressively shorter central path. This hypothesis would account not only for the continuous acceleration of beating but also the brevity of paroxysms. The events may have been modified by lack of balance between rate of propagation of the wave and recovery from the refractory phase, so that possibly two mechanisms were operating to close the gap.

For Case 1, the simple hypothesis of mechanism of offset we have suggested as applicable to Case 2 is not valid. In the longer paroxysms,

regular rate of beating was established, indicating that the excitation wave was traveling in an established circuit at a regular rate. Here the failure of the circus movement to persist is susceptible of two interpretations:

1. It may be assumed that a condition of stability is not attained because the rate of propagation of the wave allows for complete circulation in the fixed path at a rate slightly in excess of the time necessary for recovery from the refractory phase. Under such circumstances, a gap at first entirely adequate for the perpetuation of the circus movement would gradually narrow and eventually close. The closure might be abrupt or might be preceded by slight slowing as the crest of the wave encountered barriers of refractory tissue, or was forced into a longer path.

2. The second hypothesis involves the assumption of a prolongation of the refractory period of auricular muscle shortly after the establishment of the circus movement. According to Lewis,[10] prolongation of the refractory period is the mechanism responsible for the termination of the circus movement after the administration of quinidin. In the type of cases considered by Lewis, however, the circus movement was of comparatively long duration and thus conditions were not the same as in our Case 1. It is necessary in a regular circus movement of more than momentary duration that the central path must follow a course of the proper length to establish equilibrium between the rate of conduction and the rate of recovery from the refractory phase. Under such circumstances, to change the central path of the circus movement or to terminate it, there must of necessity be a disturbance of the balance between duration of refractory phase and the rate of fiber conduction.

We are unable to deny that prolongation of refractory phase following the onset of flutter may have occurred in our Case 1 and may have been solely responsible for the termination of the flutter. We have practically no knowledge of what influence pathologic changes in auricular muscle may exert on the refractory period. We wish to emphasize, however, that it is not necessary to attribute the termination of very brief circus movement to such a mechanism and regard failure to establish equilibrium between rate of propagation of the wave and refractory period as a far more likely explanation of the early termination of the circus movement.

Vagus Stimulation.—The conspicuous effects of vagus stimulation in our Case 1, namely, general tendency toward prolongation of paroxysms and increased slowing of auricular rate just preceding offset, are manifestations of vagus action not hitherto described in clinical

10. Lewis, T.: The Actions of Atropin and Quinidin in Fibrillation of the Auricles; Clinical and Experimental Studies, Am. J. Med. Sc. **164**:1 (July) 1922.

flutter. Vagus stimulation was studied by Wilson[11] in a case of paroxysmal flutter lasting for several days. In his case, distinct acceleration of auricular rate was obtained.

Lewis, Drury and Bulger[12] have found that vagus stimulation in dogs conspicuously reduces the refractory period of the auricle but has no direct effect on fiber conduction. Quickening of rate has been explained by them as due to removal of partial barriers of refractory muscle in the path of the advancing wave which had compelled it to assume a sinuous course. Acceleration of rate under such circumstances is not due to increased rate of fiber conduction, and it need not be due to the assumption of a new central circus path. Wilson favored the view that the acceleration observed in his case was due to the assumption of a shorter central circus path, this having been made possible by widening of the gap through reduction of the refractory period. Here, again, reduction of the refractory period is regarded as of fundamental importance.

The results of Lewis, Wilson and others who have observed acceleration, or even auricular fibrillation and rapid reexcitation of the auricles under vagus stimulation, are not necessarily contradictory to ours, since the former were obtained in established experimental or clinical flutter. Our results may also be explained on the basis of a reduced refractory period. If the mechanism we have proposed in explanation of the brief paroxysms in Case 1 is correct, namely, that in the circus path established, flutter is not maintained because rate of conduction is in excess of rate of recovery from the refractory phase, it is to be expected that reduction in refractory period would tend toward equalization of these functions and thus have a tendency to prolong paroxysms. Under such circumstances also, the gap would tend to close more gradually. Thus the period during which the advancing wave traveled through partially refractory tissue might be prolonged and the rate of circus movement, just prior to its termination, be more retarded. The clinical findings are in accord with these considerations.

If we accept the alternative hypothesis to account for the very brief paroxysms, namely, that they are terminated by more or less abrupt depression of the refractory period, the lengthening and more gradual offset under vagus stimulation must be regarded as due to a postponement of the depression of refractory period and to more gradual depression. There are, so far as we know, no experimental or clinical

11. Wilson, F. N.: Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, Heart **11**:61 (Jan. 30) 1924.

12. Lewis, T.; Drury, A. N., and Bulger, H. A.: Observations upon Flutter and Fibrillation. Part VII. The Effects of Vagal Stimulation, Heart **8**:141 (May) 1921.

precedents for such an action of the vagus on the refractory period, but the possibility of its occurrence cannot, at present, be denied.

The markedly prolonged paroxysm with waxing and waning of auricular rate (of which a part is shown in Figure 3, lower strip) was the most striking effect produced by vagus stimulation. The periods of slowing resemble closely the tracings of offset under vagus stimulation up to the point that acceleration begins again (compare upper and lower strips, Figure 3). Now unless it may be assumed that in diseased auricular tissue fiber conduction may be retarded by vagus stimulation (of which there is apparently no evidence) slowing must be due to narrowing of the gap between the crest and wake of the excitation wave, causing the crest to take up a more sinuous course over the same general path or else seek a new longer circuit. With such a slow circulation of the wave as was recorded, it is apparent that if the wave is permitted to continue, the gap must speedily widen since the rate of circulation is now so prolonged as to give ample time for recovery from the refractory phase. Under such circumstances acceleration of rate of beating is brought about either by removal of barriers of refractory muscle (if we assume that slowing had been due to more sinuous course of the wave over the same general path) or by re-entrance on a shorter path (if we assume that slowing had been due to assumption of a longer path).

We conclude, therefore, that the effects observed from vagus stimulation are due to reduction of the refractory period of auricular muscle. Slight reduction results in slight prolongation of paroxysms. More marked reduction results in comparatively prolonged paroxysms with waxing and waning of auricular rate. Had even greater reduction been possible, it is entirely probable that equilibrium between rate of propagation of the wave and duration of the refractory period might have been established (for the period of stimulation) and pure flutter obtained. The nearest approach to pure flutter produced by vagus stimulation was twenty cycles of regular beating.

Atropin.—It was anticipated that atropin in full physiologic dosage might exert a favorable effect on the arrhythmia, either by eliminating premature auricular beats, as it frequently does in the case of ordinary premature auricular contractions, or by shortening the periods of circus movement. The latter expectation was aroused particularly on account of the fact that vagus stimulation had been shown to prolong paroxysms. Although it has been known for a long time that atropin is capable of provoking auricular fibrillation in some experimental animals, Lewis [10] is authority for the statement that atropin is usually an effective remedy for fibrillation in dogs, and suggests that while it is not effective clinically in chronic cases of fibrillation, it might be so in more acute cases. In order to test the value of this interesting suggestion in the type of

case dealt with here, we studied the effects of both 2 and 4 mg. of atropin injected hypodermically, with practically negative results, so far as auricular arrhythmia was concerned. In this connection, however, it should be pointed out that vagal tone was probably not very great in this patient, since in spite of dilatation of pupils, impaired vision, flushing, dryness of the mouth, difficulty in swallowing and garrulity, the rate of sinus beating was not increased more than 18 per minute by atropin.

Quinidin.—The remarkable effects of quinidin both in suppressing premature contractions and terminating circus movement are familiar to all who have had experience in the use of this drug. Both effects were conspicuously exhibited in Case 1. It is of interest that the favorable action was not prolonged for more than forty-eight hours after withdrawing the drug. Such a result is what might have been anticipated in view of the rapid excretion of quinidin.

Digitalis.—We have occasionally observed either partial or complete suppression of premature auricular beats under the influence of digitalis, such as resulted in Case 1, but the inhibition of circus movement was unexpected. The complex action of digitalis on the auricle, due to the fact that its direct effect on auricular muscle and its indirect effect produced through the vagus nerve are opposed to each other, makes speculation as to the mode of its action in our case profitless. Of practical importance is the fact that of the various methods of treatment attempted, digitalis produced by far the most beneficial results. In the first case, it abolished the arrhythmia except for occasional premature beats; in the second case, it definitely lessened the arrhythmia. In both cases its use was attended by distinct subjective improvement.

SUMMARY

1. Two cases are reported, both exhibiting numerous fleeting paroxysms of slightly impure auricular flutter. This form of arrhythmia, not hitherto described, deserves rank as a clinical entity and should have reserved for it the name intermittent auricular flutter which was first applied by Ritchie to a somewhat different condition.

2. Numerous tracings of onsets of paroxysms were recorded and the variations among them pointed out. The significance of premature ectopic auricular beats in the initiation of circus movement is discussed.

3. Differences in tracing of offsets in the two cases are demonstrated, indicating differences in mechanism of offsets. An attempt has been made to account for the phenomena bringing about offsets in the two cases.

4. The effects of vagus stimulation were studied in Case 1. The most conspicuous effects were prolongation of paroxysms and exaggeration of slowing of auricular rate just preceding offset. On one

occasion there was found not only prolongation of a paroxysm but alternating periods of rapid and less rapid auricular rate. These phenomena are regarded as due primarily to reduction of refractory period of auricular muscle by vagus stimulation.

5. Atropin in full physiologic dosage exerted no significant effect on the arrhythmia in Case 1, except to improve auriculoventricular conduction. Quinidin and digitalis were both effective in suppressing the arrhythmia.

6. Digitalis in moderate dosage decreased the arrhythmia in Case 2, but did not abolish it. Following effective surgical treatment of hyperthyroidism, the arrhythmia completely disappeared.

THE SKIN CAPILLARIES IN RAYNAUD'S DISEASE *

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During the last decade, physiologic investigation has revealed many new facts with regard to the activity of the capillaries. Our knowledge is as yet fragmentary and incomplete, but enough has been learned to emphasize the great importance of this portion of the vascular system.

From the standpoint of tonus, the capillaries may be affected either by spastic or contraction reactions, or by atony or dilatation reactions. The clinical manifestations usually include a combination of these capillary responses, although pure reactions are seen. The atonic capillary is usually seen in the so-called vasoneurotic constitutional states, and less often in persons with apparently normal vasomotor mechanisms. Müller [1] has described the capillary picture in the vasomotor neuroses. This varies markedly from the so-called normal capillary. He emphasized the following points:

1. *Spastic and Atonic Reactions of the Capillary.*—The tonus of the capillary is evidenced by changes in the lumen of the vessel, either contracted or dilated. Either of these conditions may be uniformly present throughout the field, or may alternate or follow in sequence. Müller believes that these phenomena are due to inherent changes in the loops, and are not a result of arteriolar or venous reaction, since the capillary reactions are variable in contiguous loops. He holds that if changes in the arteriole lumen were responsible, tributary groups of capillaries would behave similarly.

2. *Variation in the Flow and Pressure.*—Abnormal flow is evidenced by changes in velocity, periods of stasis and granular stream.

3. *Abnormalities in Morphology of the Loops.*—The morphologic variations, he considers of less importance. Abnormally large loops and an abnormally visible capillary venous network are sometimes noted. Parrisius [2] has described the appearance of the capillaries and contained blood during the stasis periods in abnormal vasomotor states. Müller has described, in Raynaud's disease, large deformed types of loops with gaps in the stream which he attributes to capillary spasm, giving a broken up appearance of the loops.

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1. Müller, L. R.: Studien über den Dermagraphismus und dessen diagnostische Bedeutung, Deutsch. Ztschr. f. Nervenh. **47–48**:413-434, 1913.

2. Parrisius, W.: Kapillarstudien bei Vasoneurosen, Deutsch. Ztschr. f. Nervenh. **72**:320, 1921.

4. *Changes in Capillary Permeability.*—The changes in capillary permeability cannot be studied by the microscope, but are manifested by scleroderma and other metabolic and structural changes in the skin. Further information can be obtained by studying capillary reactions to different types of stimuli, such as drugs, mechanical and thermic.

In studying the form and behavior of capillaries, it is exceedingly difficult, in certain instances, to determine where the normal leaves off and the pathologic begins. In many apparently normal persons, occasional loops are short and tortuous, dilated or contracted, or are otherwise abnormal. The granular appearance of the flow or the cessation of flow, and plasma gaps, may also be observed in single loops. In the normal person, however, these are isolated phenomena. Not until the majority of the loops are abnormal in form and flow are the capillaries classified as pathologic. When a sufficient number of capillaries reveal stasis with dilatation, a definitely recognized cyanosis will exist, and when a sufficient number are empty or only partially filled, pallor of the skin will be recognized macroscopically. As Ebbecke [3] has shown, the degree of dilatation of the capillaries and venules determines the color of the skin, while arterial dilatation determines the heat of the skin. In differentiating the pathologic from the normal, the quantitative changes rather than the qualitative indicate disease. Abnormal capillaries, in the absence of clinical manifestations, are occasionally encountered.

That the capillaries have an independent contractility seems reasonable. These vessels exhibit responses perhaps more delicate than those of the larger vessels. This would be expected on the basis of structure and function. Anatomic researches have demonstrated contractile or Rouget cells with fine fibrillae wrapped about the endothelial tube. The transitional point from arteriole to capillary, or from capillary to venule, is not always well defined in the vessels of the skin. In lower orders and certain capillaries of mammals, the transitional point is definite, according to Krogh.[4] Vasoconstrictor nerves have been demonstrated for certain groups of capillaries. Sufficient confirmation of the existence of dilator fibers is not available. Dilatation of the capillaries has been shown to occur following mechanical, thermal, chemical and hormonal action. It seems reasonable to believe that future work will demonstrate a nervous control of these vessels, similar to those of the larger vessels.

VASOMOTOR NEUROSES

The so-called vasomotor neuroses include a large heterogeneous group of conditions characterized by instability of innervation in the

3. Ebbecke, U.: Die lokale vasomotorische Reaktion der Haut und der inneren Organe, Arch. f. d. ges. Physiol. **169**:1-81, 1917.

4. Krogh, August: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922. Halpert, A., cited by Krogh.

vascular system. Cold, moist skin with mild degrees of color changes, varying from marked rubor to cyanosis, usually on the hands, feet or other peripheral areas, may constitute the entire clinical picture. Associated low blood pressure, asthenic constitution, and subnormal mental and physical reactions are frequently associated. The individuals comprising this group are of the subnormal vasomotor type. Their vasomotor responses to various stimuli are usually abnormal, showing either abnormal sensitivity or abnormal reactions to certain stimuli. There is probably an underlying congenital basis for these abnormal responses on which are superimposed physical, psychic or infectious trauma, which often brings out the latent instability or abnormal lability of the vasomotor system. Buerger [5] has recently discussed the known facts with regard to the physiology of the sympathetic or vegetative nervous system in a manner to make clear many features of these little understood abnormal states. Between the mild and the extreme types of cases, observed in Raynaud's disease, are a large number of intermediate types which cannot be classified with exactitude. It seems probable that they differ only in degree, and are expressions of the same underlying pathologic condition. This broad clinical conception of the vasomotor neuroses is borne out clinically, and by the study of capillaries. Buerger questions the wisdom of too broad a grouping, and believes that the well defined syndrome, as observed in Raynaud's disease, should be retained as a clinical entity.

MATERIAL STUDIED

Eight cases, classified in two groups, form the basis of this report. Group 1 includes three cases of outspoken Raynaud's disease, characterized by marked color changes with abnormal responses to cold, trophic disturbances, varying from slight trophic excavations on the tips of the fingers to definite gangrene, and pain disturbances. Group 2 includes five cases of the more mild conditions in which there was a history of recurring local syncope in the fingers, toes or other distal parts, followed by asphyxia with mild sensory disturbances, such as tingling, burning and numbness. The abnormal or inciting action of cold in producing attacks was a marked feature in all cases in this group.

METHODS OF STUDY [6]

The capillaries were studied, according to the method of Lombard,[7] from the standpoint of shape and size, the latter quantitatively by

5. Buerger, Leo: The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924.

6. Brown, G. E.: The Normal Skin Capillary, to be published.

7. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries, and Small Veins of the Human Skin, Am. J. Physiol. **29**:335-362, 1911-1912.

measurements of the lengths and calibers of the visible loops and their numbers to the linear millimeter.[8] A stereomicroscope with magnification of 60 and 120 times and eye-piece micrometers with divisions of 0.01 and 0.0025 mm. were used for measurements. A ribbon filament lamp with heat and color filters gave adequate illumination. For finger stabilization, a small iron trough with rubber buffers was quite satisfactory. These observations were repeated, in several instances, in the periods of syncope, cyanosis and rubor. The capillary flow was studied in respect to the rates of flow in millimeters each second, and appearance and behavior of flow in the different color stages. The effects of reduced temperature on capillary flow and skin color were also studied; these will be reported separately. Photomicrographs were made in several instances, but not with exact definition, owing to length of exposure time. Dr. Sheard[9] of the department of physics has recently perfected this technic, allowing exposures of one-fiftieth second. Five other cases showing vasomotor disturbances with sclerodermal changes in the skin are not included in this report because the capillary picture was disturbed by the organic skin changes.[10] These cases will be reported in a subsequent study.

NORMAL CAPILLARIES

Sufficient observations have been made in studying normal persons of different ages to define fairly definitely the morphologic range of the so-called normal capillary[11] (Fig. 1). The studies at the Mayo Clinic have shown that the capillary undergoes involutionary changes with advancing age, probably similar to those observed in the larger vessels. The capillary apparently becomes longer;[12] the calibers are narrowed, and the increased length may manifest itself as a long, straight or a tortuous loop. The usual normal type in the young adult is the hairpin shape, fairly regular and uniform, but there are variations. Occasionally, young persons have uniformly thick tortuous loops. The absence of narrowed lumina seems to differentiate these from the pathologic tortuous types. The greatest difficulty in distinguishing diseased capillaries arises in cases in which the normal and abnormal types are present

8. The nail-fold capillaries are apparently distinctive in that practically all are constantly functioning, thus differing from those in other portions of this tissue.

9. Sheard, C.: Instantaneous Photomicrography of the Skin Capillaries in the Living Human Body, Science **10**:409-410, 1924.

10. Brown, G. E., and O'Leary, P. A.: Scleroderma, to be published.

11. Brown, G. E., and Giffin, H. Z.: Capillaries and Blood Volume in Polycythemia Vera, Am. J. M. Sc. **166**:489-502 (Oct.) 1923.

12. The increased length of the capillary may be more apparent than real, because of increased visibility of the skin with increasing age.

in about equal numbers. At best, one observes occasional cases in which no conclusion can be drawn relative to capillary morphology. The average total length of the visible capillary loop in the normal group was 0.42 mm. The average caliber of the arterial limb was 0.007 mm., and of the venous limb 0.009 mm. These are the averages of a group of 110 approximately normal persons from the age of 20 to 95 years.[13]

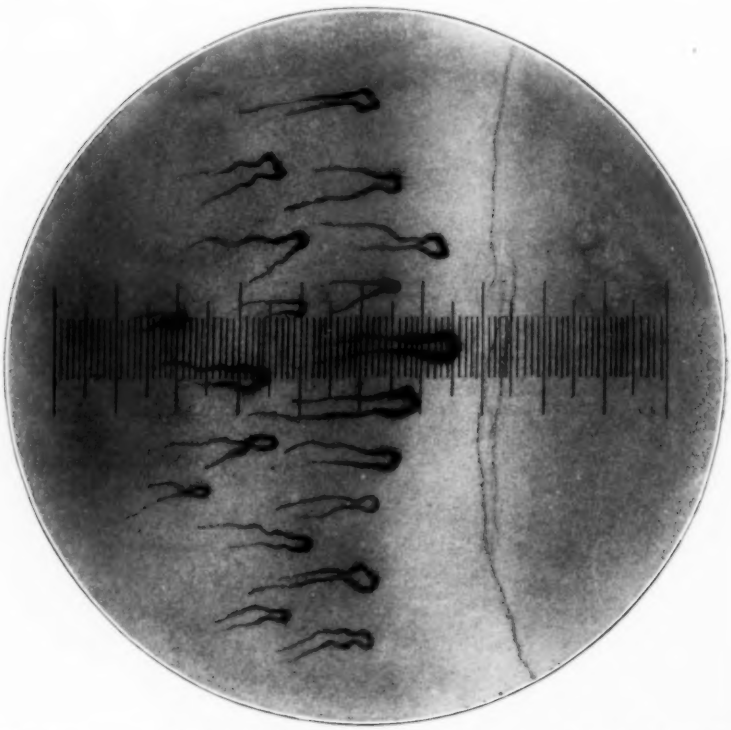

Fig. 1.—Normal capillaries. Artist's sketch; scale: smallest division, 0.01 mm.

The normality of these persons was based on the absence of demonstrable disease and normal cardiorenal vascular findings for their age.

THE "NORMAL" CAPILLARY FLOW

The capillary flow, in most loops, is usually uniform and rapid at room temperature, from 24 to 26 C. Occasionally, the stream has a

13. The measurement of the length of capillary loops is subject to a moderate error since the arterial and venous terminals are often indistinct and impossible of exact localization.

granular appearance, or there is a short period of stasis in isolated loops. Cold tends to retard the flow, and the period of stasis is longer. The average minimal rate of flow is about 1.5 mm. a second in the normal person.[14] In younger persons, the flow is too fast for measurement in most of the loops. The stream is fairly constant, but minor variations in the rate of flow are observed in neighboring loops. There is, however, a fairly well established normal range of flow under constant conditions as regarding hand level in relation to heart, room temperature, and effects of exercise. The observations were made under quite constant conditions, and at room temperature ranging from 24 to 26 C. Because of occupation, lack of care of the hands, local irritation of the skin, presence of edema, pigmentation or grime, the nail-fold vessels are occasionally obscured. Excessive manicuring may destroy the arrangement of the distal group of capillaries, making an accurate examination impossible. Usually, the fourth and fifth fingers show these effects to a much less degree. One should not form an opinion regarding the capillaries until all the fingers have been examined to see whether the type is fairly uniform. Occasionally, it is impossible to determine whether capillaries are abnormal. In studying the measurements, velocity, rates, and so forth, I have always examined all fingers, and selected an area for study which apparently is typical for the majority of the capillaries seen. Rarely, quite different types of capillaries are observed in different fingers.

EFFECT OF COLD ON CAPILLARY FLOW

The effects of heat and cold on skin capillaries are fairly well established in normals. The immediate effect of moderate heat is arterial and capillary dilatation and rapid, uniform flow. The effects of cold vary considerably in different persons. The usual effect of different ranges of lowered temperature to 15 C. is slight pallor of the capillary field, due to arterial and capillary contraction which may or may not be observed macroscopically by color changes in the skin, immediate slowing of the stream with moderately segmented appearance of flow due to plasma spaces, the cause of which will be discussed later, and stasis, absent, or very short. The presence of capillary cyanosis is dependent on the degree of capillary dilatation and the length of the period of stasis. After a variable period of recovery, a reaction takes place in which the stream becomes intermittent, showing alternating periods of rapid and slow flow. In persons subject to vasomotor instability, the cold reactions

14. Capillary flow diminishes in the latter decades of life. This value is for ages between twenty and forty years. Individuals of forty years and under show many capillaries with rates in excess of 1.5 mm. a second and cannot be measured with accuracy.

are similar but more marked, and are present or appear at higher temperatures than are observed in normal persons; in such persons, there is a relative intolerance to cold. When color reactions are present in sufficient degree to be evident macroscopically in the skin, the capillary behavior is pathologic from the clinical standpoint. In the cases of definite Raynaud's disease, the reactions are similar, varying only in degree (Fig. 2). Occasional cases of Raynaud's disease show similar stasis reactions to moderate degrees of heat.

THE CAPILLARIES IN RAYNAUD'S DISEASE

Morphologic Changes.—One feature which is fairly constant at room temperature is the presence of many wide, dilated atonic types of loops. Occasionally, huge types are seen, with a total length and caliber considerably greater than that observed in normal persons of the same age. These giant types are more common in patients with scleroderma.

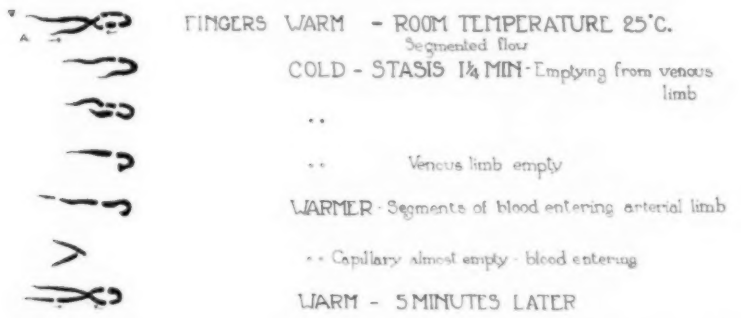
FINGERS WARM - ROOM TEMPERATURE 25°C.
Segmented flow
COLD - STASIS 1¼ MIN - Emptying from venous limb
Venous limb empty
WARMER - Segments of blood entering arterial limb
Capillary almost empty - blood entering
WARM - 5 MINUTES LATER

Fig. 2.—Observations of single capillary in Raynaud's disease, showing effect and recovery from cold.

When gangrene is present, the loops lose their characteristic form, or they may appear as shapeless thrombosed areas; differentiation is often impossible. In the average case, the venous limb is usually dilated more than the arterial limb (Table 1). The caliber of loops changes in the different color phases. I have not observed the branching types oftener than in many so-called normal cases. In the normal, there is a distinct differentiation in the caliber of the arterial and venous limb which becomes accentuated with increasing age. In Raynaud's disease, this differentiation becomes less distinct, and, in many cases, it is very difficult to distinguish the two limbs from the relative size of the calibers. The direction of capillary flow decides this point. The capillary loops at room temperature are usually of broad hairpin type, with or without tortuosity. Patients examined at 25 C. and at 15 C. show measurable differences in the diameter of the capillary lumen. With lower tempera-

Case	Condition	Age and Sex	Loops for Each Millimeter, Average	Total Length of Capillaries, Average Mm.	Average Caliber, Mm. of Arterial Limb	Average Caliber, Mm. of Venous Limb	Control Period, 25 to 25° C. Rate of Flow, Mm for Each Second	Control Period, 25 to 25° C. Description	Cyanotic Period Rate of Flow, Mm. for Each, Second	Cyanotic Period Description	Description of Capillaries
1	Advanced Raynaud's disease; marked trophic changes	52 ♂*	7	0.45	0.0125	0.015	Stasis periods for from three to seven minutes. Flow too slow for measurement			Complete stasis	Capillaries examined in nail-fold, first toe on left foot. Cyanosis 3 during warm and cold exposure; capillaries deep blue; short thick broad types; no tortuosity
2	Fairly severe Raynaud's disease; no trophic changes	28 ♂	9	0.6	0.012-0.02; average 0.016	0.012-0.02; average 0.016	0.06-0.06 0.05-0.07 0.09-0.11 Few loops; complete stasis	Granular, slow stream, few loops, stasis, many gaps or hiatuses	0.04 0.015	Stasis, or very slow segmented stream with wide gaps	Long broad loops, hairpin type; loops not well defined, ragged in outline; apparent loss of tone, much more marked during cyanosis
3	Severe Raynaud's disease; cyanosis and trophic changes	26 ♀	6	0.25	Wide caliber with broad dilated venous limbs		0.08-0.03 0.02-0.08	Few loops show complete stasis		Complete stasis in 90 per cent. of loops	Dilated broad loops, hairpin type; no tortuosity; during cold period, complete loss of tone, producing shapeless sacs
4	Fairly mild Raynaud's disease; early sclerodermal-like changes	60 ♀	..	0.56	Wide caliber; a few loops have lost their form and appear as red blotches		0.18 0.18	Many loops; complete stasis; wide gaps in stream		Complete stasis in all loops with wide hiatuses	Broad regular types; arterial limb not contracted as would be expected for a person of this age; regular hairpin types
5	Moderately severe Raynaud's disease	34 ♂	3 8	0.21	... .		0.03 0.035 0.07 0.09	Slow segmented flow; few gaps		Complete stasis for periods ranging from 20 to 40 seconds	Regular hairpin loops; many capillaries visible or segment visible; few large dilated atonic forms
6	Moderately severe Raynaud's disease; syncope and cyanosis	23 ♀	10†	0.54	Outline of capillaries too broken and ragged for accurate measurement		0.04 0.07 0.07	Slow intermittent languid flow; broken stream		Complete stasis in all loops for from 14 to 15 seconds; cyanosis disappears when flow reaches 0.07 mm. each second	Large, broad, raggede-appearing loops; many loops partly filled during stasis; many broad gaps in stream
7	Early mild Raynaud's disease; local syncope	53 ♂	6	0.70	Moderate dilatation of venous limb; arterial limb relatively contracted		0.02 complete stasis	Many loops show stasis; others very rapid flow		Complete stasis in majority of loops interspersed with capillaries showing fairly rapid velocities	No change in color of skin; history of local syncope in fingers; exposure to cold does not produce cyanosis; capillaries show vasomotor instability and tendency to stasis; loops are long, arteriosclerotic; moderately contracted arterial limb
8	Mild Raynaud's syndrome; local syncope; no cyanosis	49 ♂	12	0.22	No dilatation of arterial or venous limb		0.04 0.06 0.05	Groups of from 3 to 4 loops with slow granular stream or stasis; others with normal flow		Capillaries with different behavior in different groups of loops; flow rates slower; and few with stasis	Capillary loops resembling normal, usually with normal flow; groups of from 3 to 4 capillaries show tendency to stasis; slow granular stream and wide gaps in flow
	Average		7	0.46			0.06				
	Normal values		9	0.42‡	0.007	0.009	1.5§				

* In this table, ♂ means male, ♀ female.
† Five open and five partly open.
‡ Subject to moderate error, since exact terminals of loops cannot be determined.
§ Average flow rates in persons under 40 years of age are in excess of 1.5 mm. each second, decreasing with increasing age

tures, the outline of the loop becomes ragged and indistinct because of capillary dilatation and imperfect filling. Many loops, because of incomplete filling, appear as irregular segments. The color changes from a slight to a marked cyanosis, depending on the duration of stasis. The morphologic changes are not conclusive, and in several cases quite normal appearing loops were observed, but moderate grades of dilatation during the compensated periods were found, in some degree, in all cases in this series.

Capillary Flow.—At room temperature, the capillary loops, in practically all the cases in this series, have shown varying degrees of stasis in few or many loops, varying with the severity of the case. In other loops, the rate of flow is extremely slow, ranging from 0.02 to 0.18 mm. a second. The capillaries show varying degrees of cyanosis, depending on the duration of stasis and dilatation of the loops. Miscroscopic examination of the capillaries of certain persons, who at room temperature have practically normal skin color, reveals varying numbers of loops with marked slowing of the stream, or complete stasis. These changes were not sufficiently marked to produce color changes in the skin. This, I believe, is of important diagnostic significance, since it presupposes the presence of an abnormally labile vasomotor mechanism, which may, in the future, become of clinical importance. In the flow, there are many distinct differences from that observed in normal persons. The most striking characteristic is the slow, languid type, the presence of gaps or the plasma gaps in the capillary stream, an intermittent flow, alternating stasis and movement of the cells, and cyanosis. The cause of these clear spaces in the stream has been variously interpreted as due to capillary spasm, and waves and plasma gaps. They are apparently not due to localized spasms of capillaries, since they move in the course of the capillary stream much too rapidly for contraction. A capillary wave or pulsation would not show the intermittence of movement which these gaps exhibit. These are probably plasma spaces caused by intermittent arteriolar relaxation, which allows the cells to enter intermittently into the loops. The broken appearance of the stream apparently is not due to agglutination since it is present in the moving capillary stream and exists at the loop entrance. The flow may be seen to stop and move along at irregular intervals, and is not synchronous with the pulse, respiration or any known factor. The blood is seen to enter from the arterial side in rather languid fashion, the cells coming in clumps with clear spaces or gaps between. These abnormal types of flow are observed in single or in multiple groups of capillaries. There is no uniform rate of flow in the loops; one loop may show stasis, another slight movement. The range of velocities in all loops in the well defined cases of Raynaud's disease is much less than that observed in the normal case (Table 1). In

one patient observed (Case 8), a group of five contiguous capillaries had this intermittent granular languid flow in the compensated stage, while in the balance of the loops the capillary flow was fairly normal.[15]

BEHAVIOR AND APPEARANCE OF CAPILLARIES IN DIFFERENT COLOR STAGES

Stage of Syncope or White Stage.—The capillary loops in the syncope period are small, contracted and partially filled, with well

Fig. 3.—Appearance of nail-fold capillary in the syncope or white stage; contracted capillaries, which are more marked in arterial limb; many capillaries only partly filled or completely invisible.

defined outlines (Figs. 3 and 6). Occasional clumps of cells may be seen entering the loop from the arteriole, but in many loops no movement of blood is seen. Many loops are unfilled, and are thus invisible.

15. There is a seasonal influence on the capillary flow, the pathologic variation being less marked in summer.

The pallor of the skin is then due to many empty and partially filled capillaries with cessation of the flow in all, or in a majority of the loops. If a sufficient number of loops contain blood with stasis, these will appear cyanotic and then give a bluish pallor to the syncope stage. The transition from the stage of syncope to that of asphyxia has been observed. The loops, being either empty or partially filled, receive segments of blood from both the arterioles and venules. Large groups

Fig. 4.—Same group of capillaries as shown in Figure 3 in stage of cyanosis; increase in number of capillaries with marked dilatation in one group of capillaries; complete stasis of capillary stream with cyanosis of capillary blood.

of cells come in gradually from the arterial side, with or without a reflux of cells from the postcapillary venule. The longer the period of stasis, the more marked is the cyanosis and the greater is the dilatation of the loops. The capillary dilates with the blood, filling up the loops in a languid, desultory fashion. A loop may be filled by the blood entering in normal fashion, followed by stasis, dilatation and cyanosis.

Stage of Asphyxia.—The loops have a characteristic appearance and behavior in this stage (Figs. 4 and 6). They are large, with diameters in many loops twice that observed in the compensated period. Dilatation with complete stasis and variable degrees of cyanosis explain the color of the skin. In single loops, the blood may move extremely slowly, with one or more plasma gaps. Many loops are incompletely filled with mere

Fig. 5.—Same group of capillaries as shown in Figures 3 and 4 in rubor stage; well defined capillary outline, continued dilatation of many loops, and broken appearance of loops due to plasma gaps in four contiguous loops; capillary blood is bright red in color in majority of loops.

segments of cells. The intensity of the stage of asphyxia depends on the period of stasis and the degree of dilatation of the loops. As the period of asphyxia wears off, fairly large segments of blood may be seen entering the loops intermittently from the arteriole. The flow decreases in direct proportion as the temperature decreases. In Case 2, at 15 C., there was complete stasis with deep cyanosis in all loops. The period of stasis varies from a few seconds to twenty minutes. Symp-

toms, such as numbness, burning and tingling sensations, are complained of, and the person will make efforts to restore circulation, either by warming the hands or by exercise. The symptoms seem to have a direct analogy to those observed in the claudication states resulting from a tissue anoxemia. The transition from the cyanosis to the hyperemic period is interesting. In Figures *2* and *7* are shown the differences in the appearance of a capillary loop during the transition from complete stasis to the active capillary flow. The first movement of the stream observed was the emptying of the venous limb into the collecting venule; second, the shifting of a clump of cells in the connecting limb toward the venous side; third, a segment entering from the arterial entrance, and, fourth, an active flow from the arterial side with rapid change from a cyanotic to a bright red blood.

Fig. 6.—Capillaries in the three color stages: *A*, white or syncope stage, partially filled contracted capillaries with absence of arterial limb in several loops; *B*, blue or cyanotic stage, stasis, dilatation and plasma gaps, and *C*, red or rubor stage, sharp well defined capillary indicating partial restoration of tone and flow.

Rubor or Stage of Hyperemia.—This stage is due to the resumption of the normal flow and the presence of many moderately dilated loops and of oxyhemoglobin (Figs. 5 and 6). This is due to relaxation of arterial spasm and partial restoration of capillary tone. The capillary calibers reduce somewhat, though not to normal diameters; outlines become clearer; the stream in some loops becomes continuous, and in others shows variable speeds. This finding is not uniform, since many of the capillaries will still show varying degrees of stasis or a slow segmented flow. In other instances, alternating short periods of stasis and active flow are observed in the recovery period. There is a definite independence of capillary flow and behavior in the loops. One loop may

show complete stasis, and the next loop, normal flow. However, a fairly uniform behavior is evident in the majority of the loops. In many cases, permanent color changes are maintained in the skin, with slight degrees of rubor, cyanosis or pallor. The color transitions are rarely complete.

COMMENT

It is believed that capillaries and venules can change their lumen independently of the arteries.[16] This being true, an explanation is available for the vascular phenomena observed in certain vasomotor disorders. Hooker[17] regards the nervous control as the factor producing capillary tone to balance the chemical factors producing dilatation. Vasodilator nerves for capillaries have not as yet been demonstrated. The veins are apparently supplied with a venopressor mechanism, as shown by Hooker in his experiments on the mesenteric vessels. Other agents affecting capillary tone are metabolic and hormonal in nature. Dale's contributions on histamin have shown it to have a selective toxic action on capillary endothelium causing dilatation and inert flow in these vessels. This substance is a true capillary poison. Krogh has raised the question of the existence of a pituitary extract-like substance that exerts a tonic influence on the capillaries. Although there is much to learn with regard to the physiology of the capillaries, sufficient data is available to permit a rational explanation of the phenomena observed in these vessels in vasomotor states.

In health, there is a finely balanced coordination of the different components of the vascular tree, as evidenced by noting the effects of cold on vascular flow in the skin, the immediate effect of which is arterial constriction with diminished blood supply to the capillaries. These vessels contract synchronously, since dilated capillaries with contracted arterioles would serve no useful purpose. Compensation is evidenced by arteriole relaxation with increased arterial flow, the capillaries revealing a similar response. From observations of the venous portion of the capillary loops, it may be assumed that the venules are behaving similarly. There is a close relationship of the vegetative or sympathetic nervous system to the cerebrospinal nerves in spite of the fact that these activities are distinct. W. J. Mayo[18] has raised the question, in a recent

16. Cotton, T. F.; Slade, J. G., and Lewis, T.: Observations Upon Dermatographism with Special Reference to the Contractile Power of Capillaries, Heart **6**:227-247, 1917. Dale, H. H., and Laidlaw, P. P.: Histamin Shock, J. Physiol. **102**:355-390 (March) 1919. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamin and of Some Other Substances, J. Physiol. **52**:110-165 (July) 1918.

17. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol. **54**:30-54 (Nov.) 1920.

18. Mayo, W. J.: Coordination of Human Vegetative Functions, Surg., Gynec. & Obst. **38**:312-317 (March) 1924.

paper, whether many of the pathologic phenomena, which we interpret as evidence of nervous or functional disorders, are not the result of the more recently acquired central nervous system attempting to control the vegetative activities. It would seem possible to extend this inquiry more specificially to the vasomotor neuroses, and ask if these manifestations are not the result of an attempted control on the part of the psychic spheres. Conversely, it might be questioned whether the vegetative system might not attempt abnormal control when psychic factors apparently play no rôle. The incidence of psychic factors in precipitating the symptoms of Raynaud's disease is noteworthy. The local manifestations of blushing attest to the close interrelationship of the psychic and vasomotor activities.

The phenomena exhibited in the Raynaud type of the vasomotor neuroses indicate an abnormal sensitivity to certain stimuli, and incoordination on the part of the various components of the vascular field.

The syncope phase of an attack of Raynaud's disease is due to an excessive contraction of all three vascular elements in the skin. No blood is seen entering the capillaries; the loops are contracted and contain none or only small amounts of blood. The venules are usually invisible. The process may be quite uniform, and consists of a hyperirritable response of the vessels or the vasomotor nerves, usually, to cold, more rarely, to psychic or other stimuli. It is an exaggerated normal response. The production of color changes in the hands by the application of cold to distant portions of the body apparently proves the rôle of vasomotor nerves in this condition. There is a lowered vasomotor threshold for certain stimuli.

The stage of asphyxia reveals the loss of coordination between the capillaries and the arterioles. The arteries still remain contracted, but a reaction or intermittent relaxation has been initiated which allows small segments of arterial blood to enter the loops. The venules are apparently undergoing similar reactions since, at this stage, a reflux of blood takes place into the capillaries. This would seem to indicate intermittent contraction or relaxation of the venules. The capillaries lose their tone and dilate, the degree of cyanosis being apparently proportionate to the length of a period of stasis. The flow is static, and a high carbon dioxid content is evidenced by the change of color of the capillary blood from red to various shades of cyanosis. The dilatation seems to precede the cyanosis, apparently standing in no direct relationship to carbon dioxid content. Other metabolites may cause the loss of capillary tone. There are no data as yet to indicate the nervous mechanism in the production of the capillary dilatation. The lack of balance between the capillaries and arteries may be of physicochemical rather than nervous origin. Contraction of the venules could be assumed by the behavior of the

capillary to cold. In Figure 7 (third observation), the blood leaves the venous portion of the loop independently of movement of blood in the arterial limb. The agglutination phenomenon, as described by Krogh, apparently occurs, and segments of blood pass into the venule. Whether this indicates relaxation of venule contraction or localized capillary contraction is not clear. The former seems more likely, although Krogh does not admit the existence of contraction of the subcutaneous veins.

When the rate of flow is less than 0.1 mm. a second, a flow so slow as to include a definite period of stasis, cyanosis will be recognized in the capillary blood. This point has been designated as the threshold of cyanosis. The skin of persons with evidence of vasomotor instability, whether mild or severe, may become, at room temperature, cold, moist or cyanotic, indicating decreased arterial flow with dilatation of the

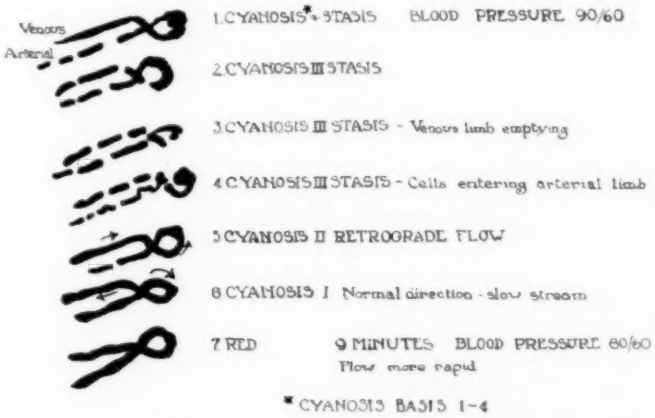
Venous
Arterial
1 CYANOSIS* + STASIS BLOOD PRESSURE 90/60
2 CYANOSIS III STASIS
3 CYANOSIS III STASIS - Venous limb emptying
4 CYANOSIS III STASIS - Cells entering arterial limb
5 CYANOSIS II RETROGRADE FLOW
6 CYANOSIS I Normal direction - slow stream
7 RED 9 MINUTES BLOOD PRESSURE 80/60
Flow more rapid
* CYANOSIS BASIS 1-4

Fig. 7.—Observations of single capillary in Raynaud's disease, showing transition from cyanotic to hyperemic stage.

capillaries, and a low cyanotic threshold. Whether the maintained loss of tonus in the capillaries and increased tonus in the arterioles is due to a nervous or physicochemical disturbance is not clear.

The presence of hypotension in the majority of such persons is interesting in the light of arteriole constriction and a consequent increased peripheral resistance. Low blood pressure is not a necessary factor in these cases, as we have observed two cases of Raynaud's disease in which there was a definite hypertension. The low blood pressure may be related to the limited area of arteriolar constrictor action, or to the decreased resistance to blood flow, due to the dilated capillary bed. The sum total of these two forces may, in terms of blood pressure, represent decreased values in the majority of instances.

The independence of capillary behavior seems reasonably certain because of the lack of uniformity of tone and flow in the contiguous loops. One capillary may show complete stasis, the next loop, normal flow, and a narrow loop, very slow flow or stasis. This individual behavior of the loops may not be entirely of capillary origin, as the precapillary arteriole and postcapillary venule may contribute to the effect. It is not certain that one arteriole always breaks up directly into a group of capillaries. What were apparently arterioles have been observed in exceptionally transparent skins, in which the precapillary arteriole was of appreciable length and was apparently tributary to one capillary. The transition of arteriole to capillary was not clearly defined. One is not justified in eliminating the precapillary and postcapillary vessels as active factors in the apparent autonomous activity of the capillaries in the skin.

In a case of Raynaud's disease, more direct visual evidence of the independent behavior of the capillary was demonstrated by the following experiment. An individual capillary was selected in which there was stasis and the loop narrow and contracted. By means of a fine glass rod, the loop was touched and dilatation preceded resumption of the flow on repeated observations. Apparently, following mechanical stimulus, and in the absence of increased intracapillary pressure, definite dilatation of the capillary takes place.

In Raynaud's [19] original description of the disease which bears his name, his explanation of the probable behavior of the capillaries fits closely with the modern explanation of the vascular phenomena. The contraction of the capillaries was assumed on the basis of clinical observation and logical conclusions drawn therefrom. He explained the appearance of the stage of asphyxia as follows:

> The vessels which return first to their normal caliber, or even beyond, are naturally those which present in their structure the fewest contractile elements, viz., the venules. At the moment when these are opened, the arterioles being still closed, the venous blood . . . flows again into the finest vascular division, and then the extremities will take on that tint varying from blue to black, which is a certain index of the presence of venous blood in the capillary network.

SUMMARY

The skin capillaries in eight cases of Raynaud's disease were studied during the different color phases exhibited by this disease. In the normal compensated periods, many of these vessels disclose evidence of disturbed capillary tone, abnormal flow or complete stasis. The degree in which these abnormalities exist determines in a large degree the color of the skin. The stage of syncope reveals many empty or partially

19. Raynaud, Maurice: On Local Asphyxia and Symmetrical Gangrene of the Extremities, Selected Monographs, London, New Sydenham Society, 1888.

filled contracted loops with stasis. The period of asphyxia is due to refilling of the capillary loops from segments of arterial or venous blood, or both, and dilatation of the loops with varying periods of stasis which determine the degree of cyanosis. The longer the cessation of capillary flow, the more pronounced is the capillary dilatation, and the greater the carbon dioxid content of the capillary blood. The recovery, or rubor phase, is due to resumption of capillary flow, more complete opening up of capillaries, pressure of oxyhemoglobin, and partial recovery of capillary tone. Additional evidence is presented to prove the existence of independent behavior of the skin capillaries.

CLINICAL STUDIES OF DIGITALIS

II. TOXIC RHYTHMS, WITH SPECIAL REFERENCE TO THE SIMILARITY BETWEEN SUCH RHYTHMS IN MAN AND IN THE CAT *

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ST. LOUIS

Numerous investigators have observed certain toxic effects of digitalis on the hearts of animals, and clinicians have assumed that the results thus recorded are generally transferable to patients. These experimental findings are not entirely constant with different species. Their importance would obviously be enhanced if it could be shown just how far the effects produced by the drug on a certain animal parallel its effects on the human heart; and it would be of especial clinical value to know in what animal the toxic effects are most like those that are produced in man. For there is no exact knowledge of the quantitative effects of toxic doses of digitalis on the human heart, because it is only when a patient accidentally receives an excessive amount of the drug that clinical records showing its toxic action are obtained. So far as knowledge acquired in this way confirms the results of pharmacologic investigation, it strengthens the inferences which experimentation affords.

The recent tendency to give digitalis in large dosage has apparently multiplied the number of instances in which toxic amounts of the drug have been administered to patients. In a recent paper,[1] I reported the therapeutic effects produced by administering rapidly large amounts of the tincture of digitalis to a series of about forty patients with normal cardiac mechanism. Toxic rhythms of short duration were observed in four of these patients. The gravity of the symptoms attendant on these toxic rhythms varied in proportion to the apparent gravity of the change in cardiac mechanism. Taken as a whole, these records present a striking parallel between the toxic effects of digitalis on the heart of man and the toxic effects which the drug has been shown to produce on the heart of the cat. The parallel is of obvious importance to experimental investigation and to clinical knowledge. It emphasizes, furthermore, the dangers that may accompany rapid digitalization. For these reasons, electrocardiograms that show certain effects of excessive quantities of digitalis on these four patients are presented, together with the accompanying clinical records.

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* From the department of internal medicine, Washington University School of Medicine.

1. Luten, Drew: Clinical Studies of Digitalis, I, Effects Produced by the Administration of Massive Dosage to Patients with Normal Mechanism, Arch. Int. Med. **33**:251 (Feb.) 1924.

Robinson and Wilson,[2] in studying the progress of events that occur when the heart of the cat is progressively poisoned by digitalis, found that there is rather a definite sequence in the manifestations of the action of digitalis on the cat's heart when successive portions of the lethal dose are regularly administered and the administration continued until death takes place. In their experiments, certain phenomena made their appearance after rather definite percentages of the lethal dose had been given. This sequence of events which represents increasing degrees of effect and of toxicity they found to be as follows: First, inversion of the T wave of the electrocardiogram occurred. After additional amounts of the drug were administered, depression of the atrioventricular conduction made its appearance. At about this time, there was some slowing of the heart rate which came on gradually. After still larger amounts, there was an increase in the rhythmicity of the auricles and of the ventricles (producing acceleration of both). The ventricular rate soon exceeded that of the auricles, thus producing atrioventricular dissociation. At about this stage, idioventricular complexes made their appearance. Independent ventricular rhythm with abnormal ventricular complexes developed. This was soon followed by ventricular fibrillation and death.

The sequence of events that followed the administration of digitalis to the four patients of my series cannot be stated with certainty, because records were not taken at sufficiently frequent intervals. An analysis of the records that were made, however, gives unmistakable evidence that this sequence is closely comparable to that which results from the toxic effects of large doses of tincture of digitalis on the heart of the cat. Certain other features of importance which have to do with the toxic action of digitalis are shown in these records, and certain conclusions regarding the toxic action of the drug on the muscle of the human heart are indicated.

In none of these patients, fortunately, did death result from the administration of digitalis, and in none was ventricular fibrillation recorded. The parallel that their records show between the toxic effects of digitalis on the human heart and those shown by Robinson and Wilson for the heart of the cat is not complete, therefore, but so far as it goes it is remarkably close.

REPORT OF CASES

CASE 1.—A man, aged 75, admitted Sept. 5, 1922, complaining principally of weakness, had had, perhaps, a little dyspnea for a year, noticeable on walking up hill. Otherwise, he had been in good health until six weeks prior to admission, at which time he noticed that he was weak and had a little fever. Fol-

2. Robinson, G. C., and Wilson, F. N.: A Quantitative Study of the Effect of Digitalis on the Heart of the Cat, J. Pharmacol. & Exper. Therap. **10**:491 (Jan.) 1918.

lowing this, he had a slight cough and sputum, also slight edema of the ankles. He had been taking 20 drops of tincture of digitalis three times a day at intervals until about a week before admission.

On admission, there was considerable cyanosis of the lips and nail beds. The cardiac impulse was rather diffuse and was inside the nipple line. The heart sounds were faint. The liver extended 8 cm. below the costal margin. There was slight edema of the legs. The peripheral arteries were considerably thickened and tortuous. The urine showed a faint trace of albumin; there were no casts. The nonprotein blood nitrogen was 31.9 mg.; the Wassermann reaction was negative; the pulse, 106; the temperature, 38.2 C. The electrocardiogram showed very small complexes in all leads, and notched Q-R-S complexes in Lead III. The provisional diagnosis was chronic myocarditis; emphysema; arterial sclerosis; passive congestion of the lungs and of the liver, and possible pericardial effusion. The patient weighed about 190 pounds (86.2 kg.).

After six days in bed, he was given tincture of digitalis as follows: September 11, 15 minims; September 12, 75 minims in four doses; from September 13 to 19 inclusive, four doses of 20 minims each every day, a total of 650 minims in eight days. During the eight days of digitalis administration he had no nausea, no change in pulse rate (the extremes being 80 and 112, the mean being 102), and there was no change in the symptoms. There was slight transitory pain in the left chest September 18 and 22. The course of the illness varied, and the patient died November 24. The necropsy showed tuberculous, serofibrinous pericarditis; about 600 c.c. of fluid in the pericardial sack; marked chronic fibrous myocarditis; calcification and occlusion of the right coronary artery; chronic passive congestion of the liver, spleen and lungs; ascites, and chronic diffuse nephritis.

The electrocardiogram, taken September 19, after 590 minims of tincture of digitalis, showed atrioventricular dissociation, the auricular rate being 90, the ventricular rate, 96. The type of complexes was essentially the same as before digitalis administration. The electrocardiogram taken the next day, after 60 minims more of tincture of digitalis, showed atrioventricular dissociation, the auricular rate being 160, the ventricular rate, 90. Digitalis had been discontinued before this record was made. The electrocardiogram taken twenty-four hours later, September 21, showed atrioventricular dissociation, the auricular rate being 93, the ventricular rate, 95. Subsequent records showed a normal mechanism, but with a lengthened P-R time, and a lowered T wave in Leads II and III for some days. There were occasional extrasystoles on admission and afterward. Digitalis apparently did not influence their frequency. Aside from the electrocardiographic records there was no indication, symptomatically or objectively, of effect from digitalis administration.

Large doses of digitalis produced atrioventricular dissociation with an auricular rate of 90 and a ventricular rate of 96. Increased dosage produced an auricular rate of 160 with a ventricular rate of 90. With subsidence of digitalis effect, the auricular tachycardia disappeared, but the ventricular rate remained high and atrioventricular dissociation persisted. With further subsidence of the effect of the drug, the mechanism became normal but showed the usual electrocardiographic evidences of therapeutic dosage. There was no symptomatic evidence of toxic or of therapeutic action of the drug.

The amount of digitalis administered was too great. It produced a serious toxic rhythm. This occurred without nausea and without any evidences of effect that could be noted at the bedside.

CASE 2.—A woman, aged 23, was admitted, Aug. 17, 1922, complaining of "dropsy," palpitation, cough and dizziness. Her illness began after a forceps delivery, three months previous to admission, with dyspnea, cough, palpitation, and swelling of the abdomen. She had been taking a "patent medicine" for two months previous to admission; but had taken no medicine from a physician in that time.

Conspicuous cyanosis, general anasarca, ascites and dulness at the bases of the lungs were noted. The liver extended 9 cm. below the costal margin. The heart was greatly enlarged. At the apex, a systolic murmur, transmitted over the precordium, and a short diastolic murmur were heard. A systolic and diastolic thrill was felt at the apex. The blood pressure was 165 systolic, 100 diastolic. The urine showed a large amount of albumin and many casts. The vital capacity was 450 c.c. The electrocardiogram on the day of admission showed auricular fibrillation and a persistent bigeminy. The ventricular rate

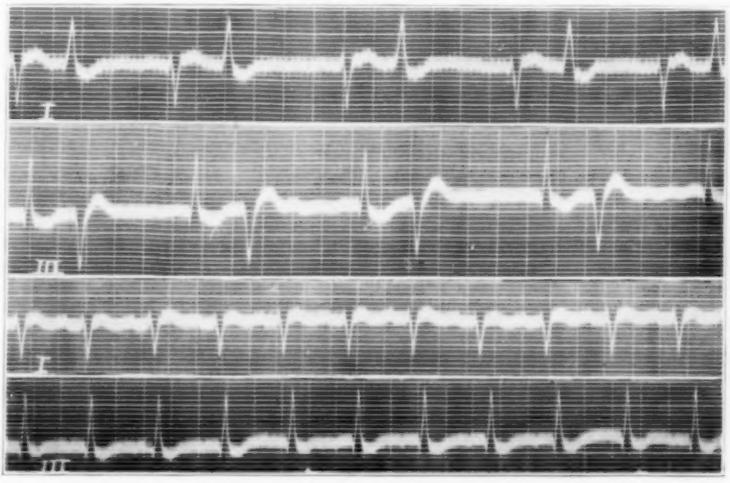

Fig. 1 (Case 2).—Upper: Leads I and III, Aug. 18, 1922, the day after admission (Lead I is distorted by extraneous current); lower: Leads I and III, August 19.

was 110. The diagnosis was cardiac decompensation; cardiac hypertrophy and dilatation; auricular fibrillation; premature contractions; mitral disease, and congestion of the liver, lungs and kidneys. The patient's weight was about 85 pounds (38.6 kg.).

Because of the electrocardiographic evidence of the action of some toxic agent, such as digitalis, on the heart, no digitalis was administered for thirty-three days. The patient made some, but not great, symptomatic improvement while at rest and on a restricted diet. The cardiac mechanism was normal, August 19 (Fig. 1, lower part), the rate being 125. Frequent electrocardiograms showed no arrhythmia thereafter until digitalis was administered. August 24, however, the rate was 144, and the mechanism appeared to be atrioventricular rhythm. The mechanism thereafter was normal; the rate remained at about 120 a minute, and the negative deflection of the T wave in Lead III became less pronounced.

September 19, the patient was given 10 c.c. of tincture of digitalis in three doses. This was followed by considerable symptomatic improvement and

lessening of the edema; there was no nausea. Eight days later (September 27), she was given 20 minims of the tincture four times daily. This was continued for a little more than five days, during which time she received 440 minims. October 2, a slight arrhythmia was noted clinically, and digitalis was stopped. There had been no nausea up to this time; but, later, October 3 and 4, moderate nausea occurred. There was considerable symptomatic improvement during the next few days, and almost complete disappearance of edema for the first time since the patient's admission to the hospital. The patient was able to be up and undertake slight exertion, leaving the hospital, October 23.

The electrocardiogram of August 17 is not suitable for reproduction. The one obtained the next day (Fig. 1, upper part) is quite similar to it, but is clearer. Extraneous current gave fine oscillations in Lead I, but Lead III, is free of this disturbance. In it the characteristic undulations of auricular

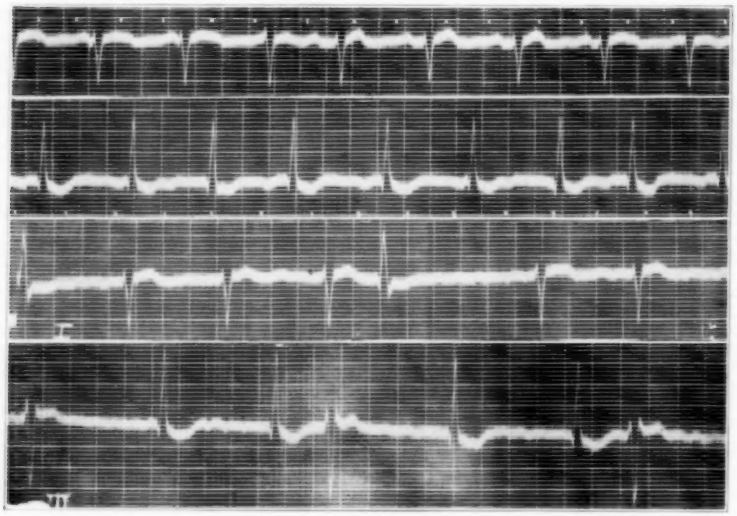

Fig. 2 (Case 2).—Upper: Leads I and III, Oct. 2, 1922, after 400 minims of tincture of digitalis in five days; auricular rate, 170; ventricular rate, 92. The position of the auricular beats is indicated by markers. Lower: Leads I and III, October 7; auricular fibrillation and frequent coupling.

fibrillation are clearly seen. There is a constant coupling. Comparison with subsequent records shows that the first complex of each couple is of the type that is "normal" for the individual. It consists, in Lead I, of a downwardly deflected Q-R-S group and an upwardly deflected T wave; in Lead III, of an upwardly deflected Q-R-S and a downwardly deflected T wave. The second complex of each couple consists of a Q-R-S group and T wave, both of which are deflected in a direction opposite to that shown in the first complex of the couple. Whether this record represents right ventricular preponderance with an extrasystole of left ventricular origin occurring after each "normal" ventricular beat—the rate of the latter being slowed by a high degree of atrioventricular block—or whether the bigeminy indicates alternate interference with conduction through the left and right branches of the atrioventricular bundle, need not be discussed here. The former would be the usual interpretation. The complexes of Lead II are similar to the corresponding complexes

of Lead III, but of smaller amplitude. The ventricular rate is 107 a minute. Next day, the mechanism was normal. For about a month thereafter and until the administration of digitalis, no abnormal mechanism was noted. The electrocardiogram of October 2, the day digitalis was stopped (Fig. 2, upper part), showed atrioventricular dissociation, an auricular rate of 170, and a ventricular rate of 92. The type of ventricular complexes was essentially the same as before. That the ventricle, though maintaining a high rate independently of the auricle, is still susceptible to auricular influence is shown in the fifth cycle of the first strip. The preceding auricular beat, appearing just before the rhythmic ventricular beat is due, stimulates a ventricular response.

This mechanism was still present on the morning of the next day, October 3, and the ventricular rate was still 92. A few days later, there was a change in cardiac mechanism, which is illustrated by Figure 2, lower part. This shows auricular fibrillation with frequent complexes similar to the second complexes of the bigeminy that was present on admission, the rate being about 82. There was no recurrence of the rhythm composed entirely of coupled beats. The auricular fibrillation persisted. The coupled beats also persisted, but their frequency diminished. The total rate increased a little.

This patient exhibited a toxic rhythm on admission. After the mechanism had been normal for a month, large doses of digitalis produced atrioventricular dissociation with an auricular rate of 170 and a ventricular rate of 92. This occurred thirty-six hours before the appearance of nausea. The dissociation and tachycardia were succeeded by a mechanism much like that observed on admission. The patient's symptoms were of a mildly toxic type, and considerable improvement followed.

The amount of digitalis administered was somewhat in excess of the optimum dose. It was enough to produce increased rhythmicity of both auricles and ventricles. These toxic signs occurred before the appearance of toxic symptoms.

CASE 3.—A man, aged 52, admitted to the hospital, Aug. 22, 1922, had been in the hospital in November, 1921, at which time his complaints were enlargement of the liver, dyspnea and pain in the upper part of the abdomen, these symptoms being of four and one-half months' duration. At his first admission, he showed Cheyne-Stokes' respiration, slight edema of the legs, and an enlargement of the liver to 15 cm. below the costal margin. The blood pressure was 190 systolic, 150 diastolic. The heart sounds were weak, the rhythm being regular except for variation with respiration. There was a faint diastolic murmur at the aortic area. The urine contained 4 gm. of albumin per liter and many granular casts. The nonprotein blood nitrogen was 57.8 mg. per hundred cubic centimeters. The vital capacity was 1,650 c.c. The diagnosis was chronic myocarditis; cardiac hypertrophy and dilatation; cardiac decompensation; chronic nephritis, and arterial sclerosis. The body weight was 190 pounds (86.2 kg.). The patient received at that time 20 c.c. of tincture of digitalis in nine hours. There was prompt diuresis; loss of weight; diminution in the size of the liver, and relief of symptoms. He was discharged greatly improved.

Following this, he had had a somewhat variable course, but, in the main, had been rather well as long as he took digitalis. For a week before his last admission, August 22, he had had some edema of the ankles, slight dizziness and, at times, a little nausea.

There was considerable edema. The liver extended about 12 cm. below the costal margin. The heart was regular. There were no murmurs. Other findings were much the same as on the first admission. The electrocardio-

gram showed a low, notched Q-R-S complex in Lead I; the T wave slightly negative in Leads I and II, and the P-R interval 0.2 second. The patient was fairly comfortable and only slightly dyspneic. The body weight was 185 pounds (83.9 kg.).

August 29, seven days after admission, he was given 5 c.c. of tincture of digitalis at 5 p. m. The next day, he received 5 c.c. at 10 a. m.; 5 c.c. at 1 p. m., and 2.5 c.c. at 6 p. m., a total of 17.5 c.c. in twenty-five hours. Before receiving the last dose, he vomited and felt worse. For a few days following digitalis administration, he was extremely uncomfortable, had almost constant nausea, and looked much worse than before. The urine output was diminished. These symptoms gradually subsided, and there was a conspicuous diuresis of increasing amounts, beginning September 4, and reaching a maximum of 4,300 c.c., September 8. The patient improved somewhat about this time, but soon thereafter began to lose ground. Uremic symptoms predominated, and he died November 24.

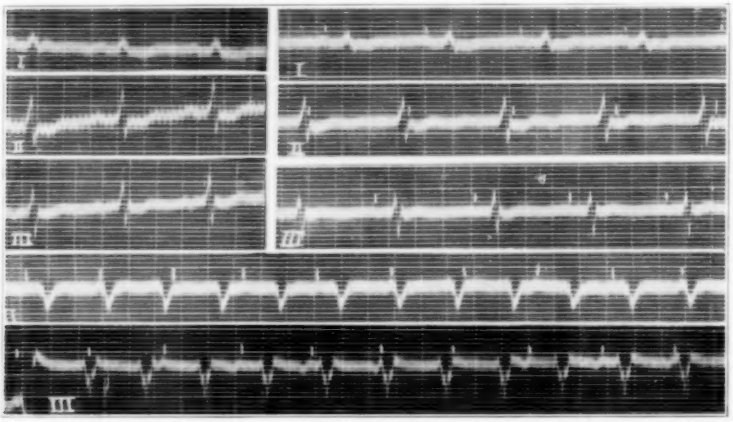

Fig. 3 (Case 3).—Upper left: Leads I, II and III, Aug. 29, 1922, just before digitalis administration; upper right: August 30, 11:20 a. m., after 10 c.c. of tincture of digitalis; lower: Leads II and III, August 31, 10:50 a. m., seventeen hours after 17.5 c.c. of tincture of digitalis; changed complexes; auricular rate, 131; ventricular rate, 162. The position of the P waves is indicated by markers.

An electrocardiogram, taken one hour and twenty minutes after the second dose of digitalis (Fig. 3, upper right), showed transient ventricular escape, the rate being 83. (This is shown only in Lead II.) Twenty-four hours later, August 31, the record shows persistent atrioventricular dissociation. The rate of the auricle was 131 a minute; that of the ventricle, 162. The form of the ventricular complexes was changed (Fig 3, lower). In other words, there was an auricular tachycardia and an independent ventricular tachycardia.

The following morning, September 1, the type of ventricular complex was similar to, but not identical with, that just described. The P waves are not clear in this curve, and the auricular rate, therefore, is questionable. The ventricular rate was 108. On the afternoon of that day, the same sort of mechanism was recorded in Lead I, the ventricular rate being 99. Lead II, however, shows an auricular rate of 65, with a ventricular rate of 99. The ventricular complexes occur rhythmically, but show striking variations in form.

September 2 (Fig. 4, top), the type of ventricular complex was essentially the same as that which had obtained since August 31. No P waves are visible, and probably both auricles and ventricles were responding to a center in the junctional tissues. Two days later (Fig. 4, second strip from top), the type of complex had changed back to the "normal" form, but visible auricular complexes were still absent. The rate, however, had slowed to 87.

The record of September 7 (Fig. 4, lower), showed atrioventricular dissociation, with complexes of the original type. There had been further slowing of the ventricle to 77, and of the auricle to 52. On the succeeding day, the mechanism was normal.

This patient, who had previously shown a remarkable improvement after taking 20 c.c. of tincture of digitalis, was given 17.5 c.c. within twenty-five hours. There was transient ventricular escape after 10 c.c. Through error, 2.5 c.c. was given after the patient had vomited. He showed symptoms of severe toxemia. Electrocardiograms showed the

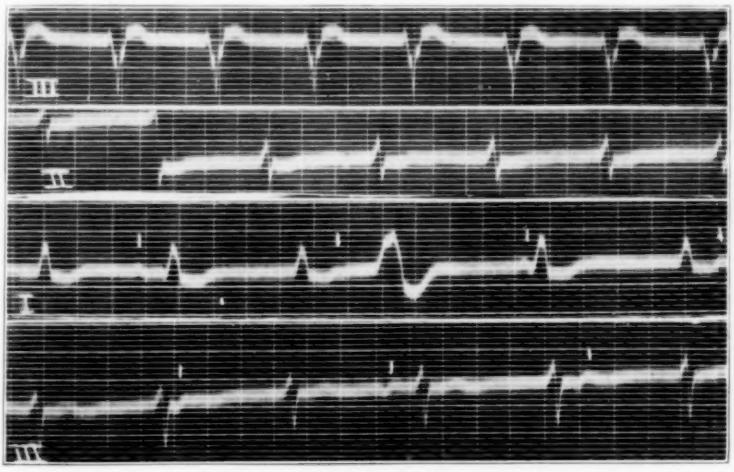

Fig. 4 (Case 3).—First strip: Lead III, Sept. 2, 1922; rate, 97; second strip: Lead II, September 4; change in complex to original type; rate 87; third and fourth strips: Leads I and III, September 7, atrioventricular dissociation; auricular rate, 52, and ventricular rate, 77.

following succession of events: (a) ventricular escape, rate 83; (b) independent ventricular tachycardia, rate 162 with a coincident auricular rate of 131; (c) atrioventricular rhythm, rate 108; (d) artrioventricular rhythm, rate 99, with a quick change to an auricular rate of 65—the ventricular complexes still occurring at a rate of 99 and showing changing forms; (e) atrioventricular rhythm with slowing rate, the type of complex changing back to the original form; (f) further ventricular slowing (77) and atrioventricular dissociation with an auricular rate of 52, and (g) normal mechanism, rate 88.

This was an alarmingly toxic dose. The rhythmicity of the auricles and of the ventricles was increased; that of the latter to such an extent that they instituted an independent rhythm. There was a vagus stimulation, but, in spite of this, the rate of the auricles and of the ventricles was usually high. With increasing elimination of the drug, the heightened rhythmicity of ventricles and auricles lessened; vagus stimulation passed off, and the pacemaker again assumed control.

An independent ventricular rhythm, associated with abnormal ventricular complexes and a rapid rate, is often a precursor of ventricular fibrillation. This result followed, in Robinson and Wilson's experimental work on cats, after the administration of little more of the drug than enough to produce such evidences of intoxication as were shown by this patient.

Case 4.—A woman, aged 46, admitted, Oct. 24, 1922, complaining of dyspnea, edema, dizziness and palpitation, had had slight dyspnea for six years, but only for the past four months had it been very great. During this time, the other symptoms had developed. She had been in bed for two weeks. For three or four weeks prior to admission, she had had no medicine except a "patent" cough remedy.

She was quite dyspneic. There were cyanosis of the lips, considerable edema of the legs and of the abdominal wall, and signs of a small amount of fluid in the right pleural sack. The heart was greatly enlarged to the left. There was a faint systolic murmur at the left sternal border and at the aortic area. There was also a suggestion of gallop rhythm. The urine contained a large amount of albumin and many granular casts. The nonprotein blood nitrogen was 47.7 mg. per hundred cubic centimeters; the vital capacity, 800 c.c.; the blood pressure, 115 systolic, 95 diastolic. The body weight was 190 pounds (86.2 kg.). The electrocardiogram (Fig. 5, upper left) showed ventricular complexes rather low in all leads, and notched in Lead III, the rate being 96. The diagnosis was cardiac decompensation; chronic myocarditis; cardiac hypertrophy and dilatation, and chronic nephritis.

The patient improved a little during eight days observation, and was then given tincture of digitalis as follows: 10 c.c. at 8 p. m., November 1, 3 c.c. at 8:30 a. m., November 2, and 3 c.c. at noon, November 2. There was an early diuresis beginning on the night of the 1st. Beginning with the night of the 2d, the patient had considerable nausea and vomiting for thirty-six hours. There was no symptomatic improvement for seven days. After this period, she gradually improved and left the hospital, November 28.

The electrocardiogram, taken ten minutes after the last dose of digitalis and, therefore, before its effect on the heart, shows a lengthened P-R interval and a sinus rhythm with a rate of 145 (Fig. 5, lower). This was higher than any rate recorded before digitalis administration.

Figure 6 shows portions of the record made at 10:30 a. m., November 3, twenty-two and one-half hours after the last dose. The three leads were recorded, and immediately thereafter a second record of three leads was made. When the first part of the first of these records was recorded, the auricles were beating rhythmically at a rate of 160, while the ventricles were beating arrhythmically at a rate of 96. There was not complete dissociation, however, between auricules and ventricles, for there were three ventricular responses to every five beats of the auricles. Two out of every five of the auricular contractions produced no ventricular response, while three were able to stimulate the ventricles to contract. The shapes of the three ventricular complexes

follow a certain sequence. The form of the first two is normal, while that of the third is aberrant. The P-R intervals also follow a certain sequence. The interval preceding the first of the normal ventricular complexes is about 0.2 second, that preceding the second is about 0.17 second, while that preceding the abnormal complex is about 0.22 second. These abnormal ventricular complexes, then, are not due to premature ventricular contractions, as might, at first glance, be inferred. Their abnormal form is due to imperfect recovery of the ventricular conducting tracts; the prolonged P-R interval preceding these abnormal complexes is due to a similar defect in the junctional tissues.

Still further evidence of depressed intraventricular conduction is given in that part of the curve recorded later (Fig. 6, lower part). The first part of the third strip of this figure shows the same sequence of events which has just been described. The aberrant complexes are of a form which suggests interference with conduction in the *right* branch of the bundle.[3] At the point marked

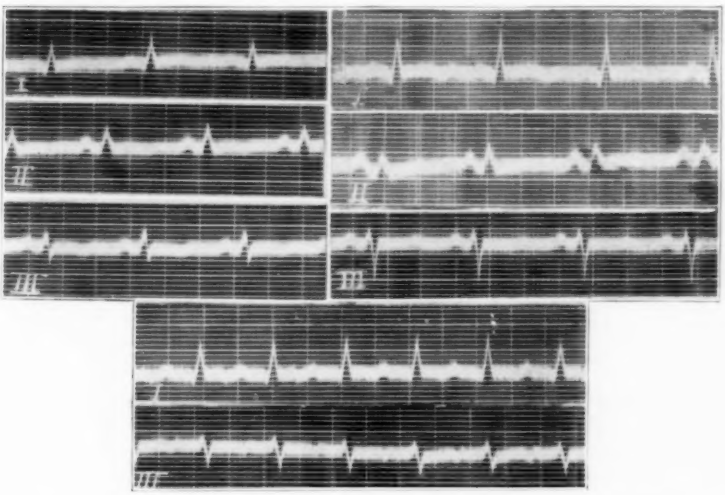

Fig. 5 (Case 4).—Upper left: Leads I, II and III, Oct. 25, 1922, seven days before giving digitalis; rate, 103; upper right: November 1, three hours before; rate, 96; lower: Leads I and III, November 2, ten minutes after last dose of digitalis; rate, 145.

R_2, the ventricular complex is of different type. It has the general outline of those complexes produced by defect in conduction through the *left* branch of the bundle. Following this are two aberrant complexes which indicate an alternation in the facility with which the two branches of the bundle conducted impulses (R_3 and R_4). Further on (R_5), the left branch again is at fault, and, after two more beats, the shapes of the succeeding complexes (R_6, R_7 and R_8) indicate again an alternation in conduction through the two branches.

These records also show that, for a short time, this patient exhibited an independent ventricular tachycardia. The ventricular rate was 145, the auricular

3. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920; An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229 (May) 1921.

rate 170 (Fig. 6, second strip). The shape of the complexes is different from that shown before digitalis administration, and they occur rhythmically.

Tachycardia was observed clinically at intervals for two days following the administration of digitalis. For the third to the seventh days, inclusive, the highest recorded pulse rate was 105, the mean being 90. The next record, taken seven days after the last dose of digitalis, shows complexes of substantially the same form as those recorded just before the drug was given.

This woman, weighing 190 pounds (86.2 kg.), with considerable edema, myocardial insufficiency and chronic nephritis, received 16 c.c. of tincture of digitalis within sixteen hours. There was an early diuresis. This was followed by nausea and vomiting for thirty-six hours. During the next week, she showed no symptomatic improvement. While the patient exhibited toxic symptoms, the following electrocardiographic effects were shown: Auricular tachycardia, rate 160 to 170; partial block

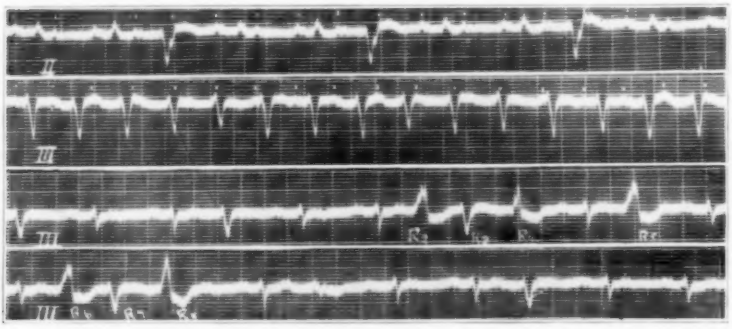

Fig. 6 (Case 4).—Nov. 3, 1922, twenty-two and one-half hours after the last dose of digitalis; Lead II (first strip) shows an auricular rate of 160 with a ventricular rate of three-fifths as much, i. e., 96; long atrioventricular time preceding aberrant ventricular complexes. In the second strip (Lead III), the rate of the auricles is 170, that of the ventricles, 145; position of auricular waves is indicated by markers. The third and fourth strips are a continuous record in Lead III; alternation in direction of complexes R_2, R_3 and R_4, and of complexes R_6, R_7 and R_8.

with certain atypical ventricular complexes apparently due to depressed intraventricular conduction; auriculoventricular dissociation with an auricular rate of 170 and an independent ventricular tachycardia, rate 145, and depression of conduction through the bundle branches with alternate recovery of the right and left branches. After partial elimination of the drug, the cardiac mechanism returned to normal.

A beneficial effect was shown after the first dose of 10 c.c. There was a prompt diuresis. Following the additional amounts of digitalis, the ventricular tachycardia and the interference with intraventricular conduction gave evidence of serious intoxication of the heart muscle.

COMMENT

These four patients all developed auricular tachycardia as a result of digitalis administration. Two of the four showed, coincidently with this auricular tachycardia, ventricular rates between 90 and 100, with complexes of supraventricular form. The other two showed idioventricular tachycardia with abnormal ventricular complexes, the ventricular rates being 145 and 162, respectively. These two patients, who exhibited independent ventricular rhythms with abnormal ventricular complexes, manifested symptoms of much greater severity than the symptoms shown by the two others. It would appear, therefore, from a consideration of these four cases, that toxic doses of digitalis produce on the human heart, when administered in increasing amounts, the following sequence of abnormal mechanisms: auricular tachycardia; increase in the ventricular rate until it exceeds the auricular rate, and independent ventricular tachycardia with abnormal complexes.

The quantitative effect of toxic doses of digitalis on the human heart, it will be observed, closely parallels thus far its quantitative effect on the heart of the cat. Robinson and Wilson [2] further observed changes in the type of the ventricular complexes, and, finally, ventricular fibrillation. These changes in form of the ventricular complex they interpret as being the expression of impulses arising at different foci. Our patients who exhibited signs of severe toxemia and at the same time showed independent ventricular rhythm gave records which contained also evidence of impaired intraventricular conduction. There is abundant evidence that drugs of the digitalis group do produce such depression of conduction within the ventricle. Robinson and Bredeck [4] gave this interpretation to the changing ventricular complexes that were recorded in a patient ten minutes after an injection of 1 mg. of strophanthin. They further say that this record "is similar to those obtained by Levy and Lewis during this period of so-called potential (ventricular) fibrillation."

Wilson and Robinson,[5] in commenting on "spontaneous change in the form of the ventricular complex" shown by a patient with complete heart block twenty-three hours after a massive dose of digitalis, offer two possible explanations of the distorted complexes: (a) a change in intraventricular conduction, or (b) a change in the location of the pacemaker. It is not always possible to determine which of these causes operates to produce changes in the form of ventricular complexes. Levy and Lewis,[6] indeed, interpret their curves, to which Robinson and

4. Robinson, G. C., and Bredeck, J. F.: Ventricular Fibrillation in Man with Cardiac Recovery, Arch. Int. Med. **20**:725 (Nov.) 1917.

5. Wilson, F. N., and Robinson, G. C.: Two Cases of Complete Heart Block Showing Unusual Features, Arch. Int. Med. **21**:166 (Jan.) 1918.

6. Levy, A. G., and Lewis, T.: Heart Irregularities, Resulting from the Inhalation of Low Chloroform Vapor and Their Relationship to Ventricular Fibrillation, Heart **3**:99 (Oct. 30) 1911.

Bredeck make reference, not as evidence of depressed conduction, but as premature contractions arising from a number of separate foci. In our patients, however, the evidence is very strong that the change was produced by variation in conduction through the bundle branches. In either case, the abnormal ventricular complexes shown in our records are an expression of a highly toxic action of digitalis on the hearts of these patients, and the parallel to the action of the drug on the cat's heart is thus extended. The production of ventricular fibrillation, if additional doses are administered after ventricular tachycardia with abnormal complexes makes its appearance, is probable.

SUMMARY

1. Four patients with normal cardiac mechanism developed temporary auricular tachycardia and atrioventricular dissociation after receiving large amounts of digitalis. The ventricular rate was more than 90 in all four cases. In two cases, the ventricular rate was more than 140.

2. The quantitative effects of large toxic doses of digitalis on the human heart thus closely parallels the quantitative effects of the drug on the heart of the cat in increasing the rhythmicity of cardiac muscle.

3. The records of the two cases with independent ventricular tachycardia gave evidence also of impaired conductivity through the bundle branches. This evidence of impaired conductivity within the ventricle gives further support to the view that the effect of additional dosage further parallels the effect shown on the cat's heart in producing ventricular fibrillation.

519 University Club Building.

CLINICAL STUDIES OF DIGITALIS

III. ADVANCED TOXIC RHYTHMS *

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ST. LOUIS

In giving large amounts of the tincture of digitalis to a series of patients with normal cardiac mechanism,[1] I observed auriculoventricular dissociation with tachycardia of auricles, of ventricles, or of both, as a toxic effect of the drug in four patients. A comprehensive study of these toxic rhythms [2] showed a remarkably close parallel quantitatively between the effects in these patients and the toxic effects which were observed by Robinson and Wilson to result when successive fractions of the lethal dose were administered to cats. These authors found that further dosage produced ventricular fibrillation. The drug was stopped about the time of the appearance of these abnormal rhythms in my patients, and further harmful effects, fortunately, were not observed.

While the study of these effects of digitalis was in progress, there were published several reports of abnormal cardiac mechanisms occurring in patients who had been receiving large amounts of digitalis. One peculiar form of ventricular tachycardia, in particular, was reported by Schwensen [3] and by Felberbaum.[4] This consisted in a regular tachycardia with an alternate change in the direction of deflection of the Q-R-S complexes. Felberbaum suggested the possible rôle of digitalis as a cause of this unusual mechanism, while Schwensen expressed the conviction that the drug was the causative agent. Possible explanations of the exact mechanism by which this regular alternation in direction of the complexes might be produced were discussed by both authors. The likelihood of its transition into ventricular fibrillation was emphasized by both.

My own observations on the action of digitalis in producing ventricular tachycardia, referred to above, led me to believe that this

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* From the Department of Internal Medicine, Washington University School of Medicine.

* Read before the Central Interurban Clinical Club, Dec. 1, 1923.

1. Luten, Drew: Clinical Studies of Digitalis, I, Effects Produced by the Administration of Massive Dosage to Patients with Normal Mechanism, Arch. Int. Med. **33**:251 (Feb. 15) 1924.

2. Luten, Drew: Clinical Studies of Digitalis, II, Toxic Rhythms, with Special Reference to the Similarity Between Such Rhythms in Man and in the Cat, Arch. Int. Med. **35**:74 (Jan.) 1925.

3. Schwensen, Carl: Ventricular Tachycardia as a Result of the Administration of Digitalis, Heart **9**:199 (April 30) 1922.

4. Felberbaum, David: Paroxysmal Ventricular Tachycardia; Report of a Case of Unusual Type, Am. J. M. Sc. **166**:211 (Aug.) 1923.

unusual type of tachycardia was but a more advanced effect of the drug than that shown in the patients of my series.[2] Certain portions of some of the records of my cases presented evidence which seemed to furnish, if not indeed to anticipate, an explanation of that action of digitalis by virtue of which the peculiar tachycardia in question might be produced.

In order to study these questions further, search for similar electrocardiograms was instituted among the records of the heart station of the Washington University School of Medicine at Barnes Hospital. Only two were found which were similar in every respect to the records under consideration. A third showed an alteration in direction of the ventricular complexes, but the latter were not entirely rhythmic. (This record is similar to that in another case reported by Schwensen as due to digitalis intoxication, and is somewhat comparable also to certain portions of some of the records of my patients to which reference has just been made.) The histories of the three patients from whom these electrocardiograms were obtained were then consulted. In each case, it was found that the patient had received large amounts of digitalis just before the onset of the abnormal rhythm. All three patients died within a short time after its appearance. The evidence grows more convincing, therefore, that the abnormal mechanism in these three patients, as well as that in the cases reported by Schwensen and by Felberbaum, was induced by digitalis. Still further weight was given to this conclusion, after the study was finished and while the results were being prepared for publication, in a report by Reid.[5] He published an electrocardiogram which shows the transition of a ventricular tachycardia of not unusual type into one with an alternation in the direction of the complexes. This was followed in less than thirty seconds by ventricular fibrillation and death. The patient had just been given digitalis in large amount.

A solution of the second problem, i. e., an explanation of the mechanism which produces this tachycardia with alternation in direction of complexes, is not so easy to reach, and any conclusion in the light of present data would seem to be equivocal. This study, however, affords certain observations which appear to be of importance in trying to reach an understanding of the mechanism by which digitalis produces this peculiar tachycardia. These observations will be presented and briefly discussed below. Preceding this discussion, the histories of the three patients will be given as clearly as their records allow and their electrocardiograms, which exhibit this abnormal mechanism as well as other toxic effects of digitalis, will be shown.

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5. Reid, W. D.: Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, Arch. Int. Med. **33**:23 (Jan. 15) 1924.

REPORT OF CASES

CASE 1.—A woman, aged 64, admitted to the hospital, Feb. 7, 1921, gave as her chief complaints dyspnea and edema. She had never had rheumatism. For several years, she had had attacks of dyspnea on exertion. For six weeks prior to entrance, she had had increased dyspnea as well as orthopnea and edema.

She was cyanotic. The heart dulness extended 14 cm. to the left in the sixth intercostal space. The apex rate was 115; the pulse rate, 73. The rhythm was absolutely irregular. The first sound was impure at the apex, the second sound was followed by a short blowing murmur. The diagnosis was cardiac decompensation; chronic myocarditis; hypertrophy and dilatation of the heart;

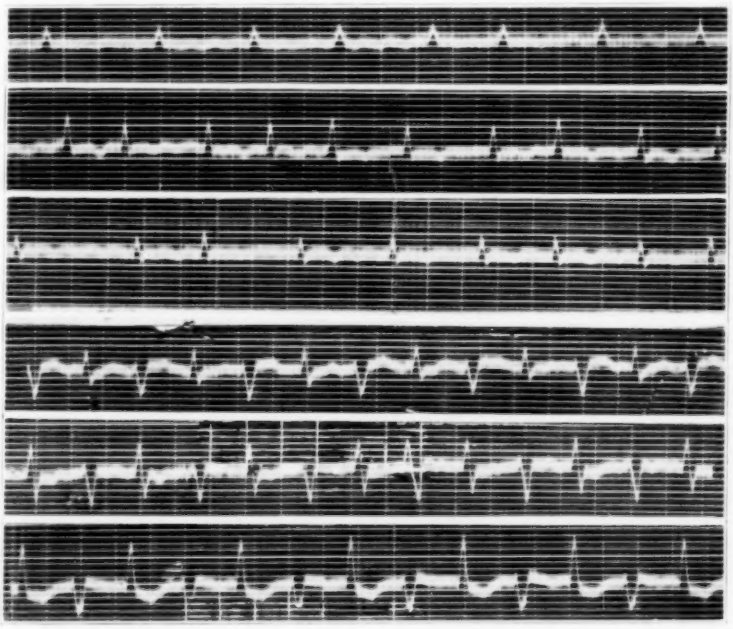

Fig. 1 (Case 1).—Upper: Leads I, II and III of the record made, Feb. 7, 1921, before digitalis administration; lower: the three leads the next day, thirteen hours after the administration of 10 c.c. of tincture of digitalis.

auricular fibrillation; hydrothorax, right and left, and edema. At 3:30 p. m., the day of admission, the electrocardiogram shown in the upper half of Figure 1 was made. It shows the characteristic features of auricular fibrillation.

The history does not give a clear picture of the patient, but it records that at 7 p. m., the day of admission, she was observed to have pinpoint pupils, slow and irregular respirations (six to eight a minute), and that this condition was thought to be due to morphin. She was given caffein sodiobenzoate, 7½ grains (0.48 gm.), and strychnin, 1/30 grain. These drugs were repeated in the same dosage, after forty minutes. At 8:30 p. m., she received 1 grain of a proprietary digitalis preparation. The notation was made that this "equals 2 c.c. of standard tincture." At 9:30 p. m., she received 7½ grains (0.48 gm.) of caffein sodiobenzoate and 1/30 grain of strychnin. The apex rate was then

150, the pulse rate, 70. At 10 p. m., the respirations were still slow and irregular. At that time, she was given 10 c.c. of tincture of digitalis. The next morning at 11:15 (February 8), the electrocardiogram shown in the lower part of Figure 1 was made. At noon it was noted that her breathing was "more regular, 25 to 28 per minute." The heart rate was 200; the pulse at the wrist, imperceptible. At 9 p. m., the same day, she received 5 c.c. of tincture of digitalis. It was noted at that time that she was in a deep stupor, and that the edema had apparently increased. Subsequent notes are fragmentary. The patient died at 7:50, the following morning.

Only the two electrocardiograms shown in Figure 1 were made. The one that was made subsequent to the administration of 10 c.c. of tincture of digitalis shows a regular tachycardia with a rate of 190. The auricular fibrillation still persists. The ventricular complexes are deflected alternately upward and downward. This record is similar to that shown in Schwensen's second case, and to the one shown in Felberbaum's case. It was this similarity which attracted attention and caused me to go over the history so as to discover whether the patient had received a large amount of digitalis just before the making of the electrocardiogram. It may be mentioned here that this exact type of curve has been recorded clinically, so far as I am aware, only in patients with auricular fibrillation who had just received large amounts of digitalis.

CASE 2.—A woman, aged 44, admitted to the hospital, Feb. 1, 1922, had as the chief complaints shortness of breath, rapid heart beat and nervousness. She had had a goiter for six years. During the six months prior to admission, she had been worse and had developed edema and ascites.

All lobes of the thyroid were prominent. There was considerable enlargement of the cardiac outline. The rhythm was absolutely irregular, rate 182. There was moderate edema, and also evidence of ascites. The diagnosis was cardiac decompensation; chronic myocarditis; hypertrophy and dilatation of the heart; auricular fibrillation and exophthalmic goiter.

The history makes no statement regarding previous digitalis administration. She was given 6 c.c. of the tincture in three doses, the day of admission. The drug was continued, 4 c.c. a day, until February 3, at which time she had received 12 c.c. It was stopped for twenty-four hours, and then again given, 3 c.c. a day. It is not clear from the record whether it was stopped on February 8 or 9. She had received 24 c.c. on February 8.

The patient's exact condition is not clearly pictured by the history, but definite statements are made that she was improving, February 4 and 6. She began to grow worse, about February 8. She "gradually became weaker," "breathing" became "difficult," and oxygen was administered February 9. There were indications of pneumonia. The patient died, the morning of February 10. No necropsy was obtained.

The electrocardiogram shown in the left upper part of Figure 2 was made, February 2, after the patient had had 8 c.c. of tincture of digitalis.

It shows auricular fibrillation with a ventricular rate of about 200 a minute. There had been a few extrasystoles. None was noted, February 4; they were rare, February 6. The right upper part of Figure 2 shows the record of February 7. The ventricular rate had declined to about 150, but the number of extrasystoles had increased. The lower part of this figure gives the record made February 8, about the date when the patient began to grow worse. She was still receiving digitalis at this time. The record shows a ventricular rate of about 125. But it shows also numerous extrasystoles. These occasionally are strongly suggestive of coupling.

The electrocardiogram shown in the upper part of Figure 3 was made at 11 a. m., February 9; that in the lower part was made at 6 p. m., the same day. The earlier record shows abnormal ventricular complexes of widely different shapes. The total ventricular rate is about 165. The later record

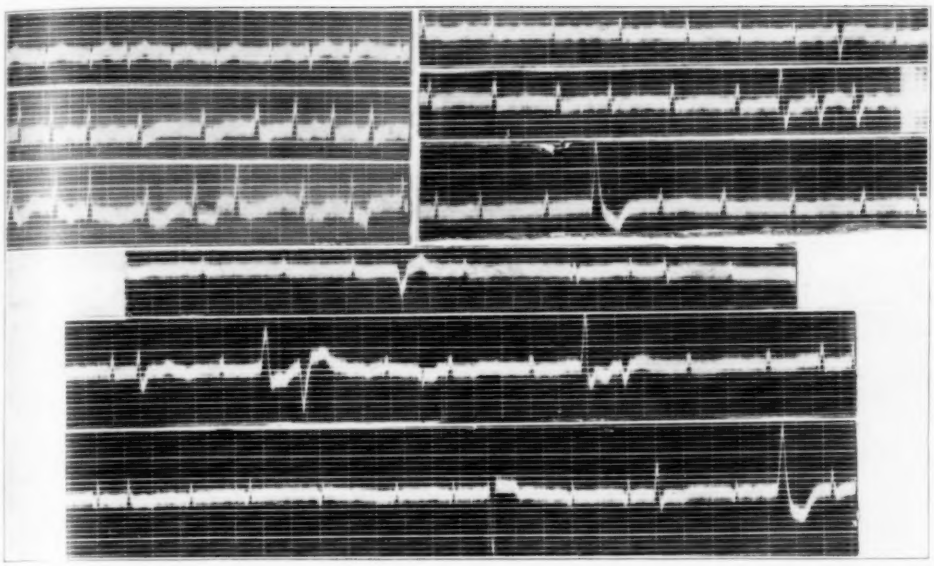

Fig. 2 (Case 2).—Upper, left: record made, Feb. 2, 1922, after 7 c.c. of tincture of digitalis in twenty-four hours; upper, right: record, February 7, after 21 c.c. of tincture of digitalis in six days; lower: record, February 8, after 24 c.c. of tincture of digitalis in seven days.

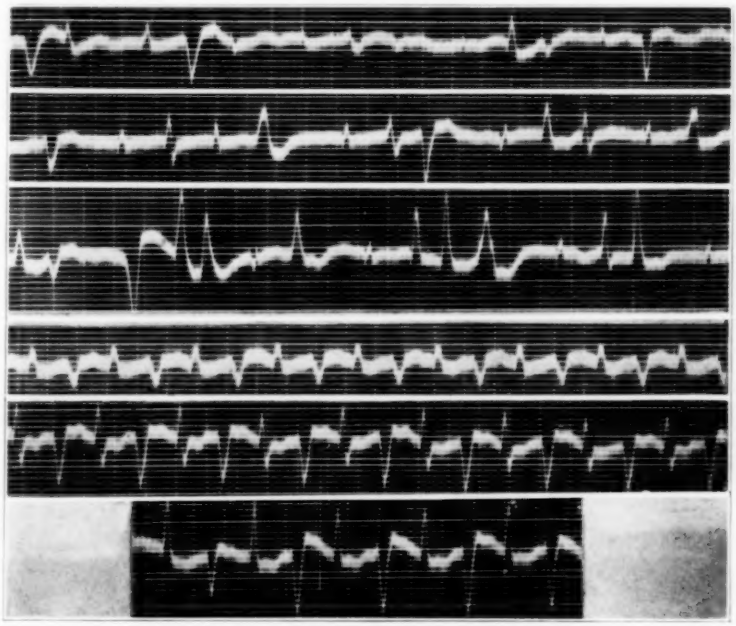

Fig. 3 (Case 2).—Upper: the three leads, February 9, at 11 a. m.; lower: the three leads the same day, at 6 p. m.

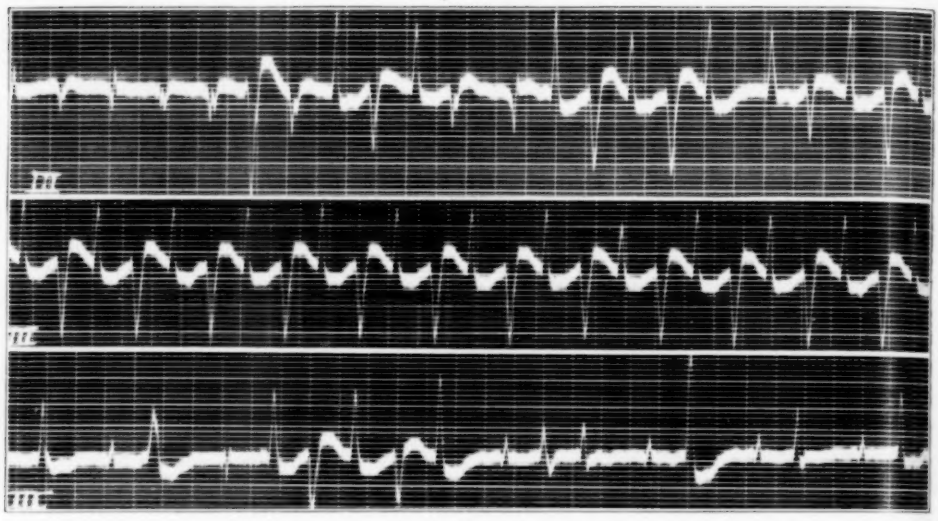

Fig. 4 (Case 2).—Lead III, night of February 9.

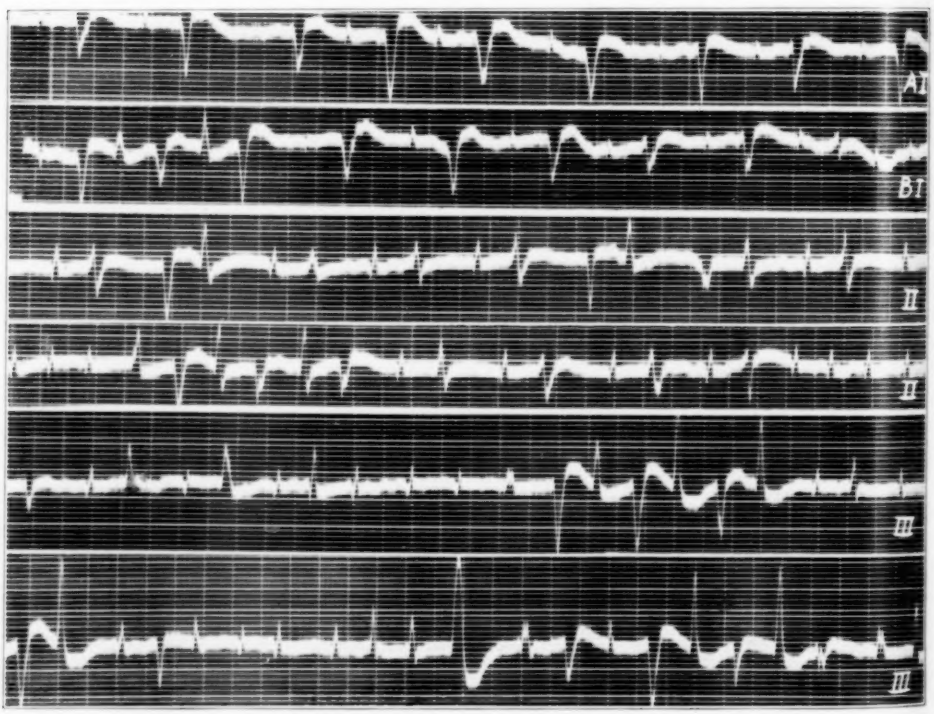

Fig. 5 (Case 2).—February 10, 9 a. m., first two strips, a continuous record in Lead I; third and fourth strips, in Lead II and fifth and sixth, in Lead III.

(lower part) shows a rhythmic tachycardia with alternation in the direction of the ventricular complexes. The rate is 220 a minute. This record is another example of the unusual mechanism in question.

Subsequent electrocardiograms were made at frequent intervals until the patient's death, the next morning. These show periods of the regular alternating tachycardia of varying lengths. Other portions of the curves show a mechanism which is similar but in which certain differences occur. These include the following: (*a*) The alternate deflections may not be invariably of opposite direction (Fig. 4, top strip); (*b*) The complexes, while alternating regularly in direction, may show variations in shape (Fig. 5, second, fourth and sixth strips). Other portions show bigeminy which is frequently of considerable length (Fig. 4, third strip). The space between the first and second component of the pairs is constant in places and constitutes true coupling. The

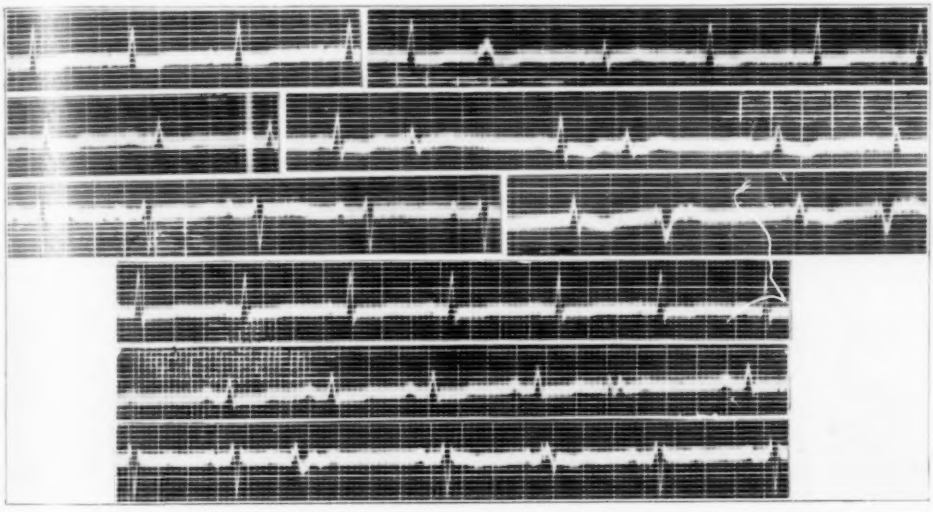

Fig. 6 (Case 3).—Upper: portions of the three leads, the day of admission, Sept. 13, 1920; lower: the three leads at 11:30 a. m., September 20, one and one-half hours before the administration of 19 c.c. of tincture of digitalis.

shapes of both components of the couples frequently undergo considerable changes (Fig. 5, first and second strips). Still other portions of these curves show isolated couples which are quite similar to the complexes of the alternating tachycardia (Fig. 5, third strip).

Case 3.—A man, aged 71, admitted to the hospital, Sept. 13, 1920, complained of dyspnea, ascites and edema of the legs. These symptoms had been present at intervals for about a year.

His general condition was "fair." There was marked edema; the liver extended 5 cm. below the costal margin; the heart sounds were clear but weak. The cardiac dulness extended 17 cm. to the left. There were many extrasystoles. The vital capacity was 1,700 c.c. The blood pressure was 150 systolic, 100 diastolic. The urine contained a large amount of albumin and many hyaline casts. The nonprotein blood nitrogen was 44.4 mg. per hundred cubic centimeters. The patient's weight was 148 pounds (67.1 kg.).

There was no notation as to whether he had or had not recently received digitalis, but the history states that "heart medicine" had "relieved edema and ascites in the past." The following summary is taken from the history: The patient was kept quiet in bed with morphin and atropin or codein for the first five days without much reduction of the edema. The size of the calf of the leg was reduced from 35 to 33 cm. The signs of hydrothorax became more pronounced. The weight dropped only 2.2 kg. On the fifth day, he was given 0.3 gm. of theophyllin every three hours for three doses. This produced no result, the patient gaining 1 kg. in one day.

On the seventh day after admission, the patient was given a massive dose of digitalis (19 c.c. of tincture of digitalis). One and a half hours later, he showed pulsus alternans.[6] Three and one half hours after administration, the

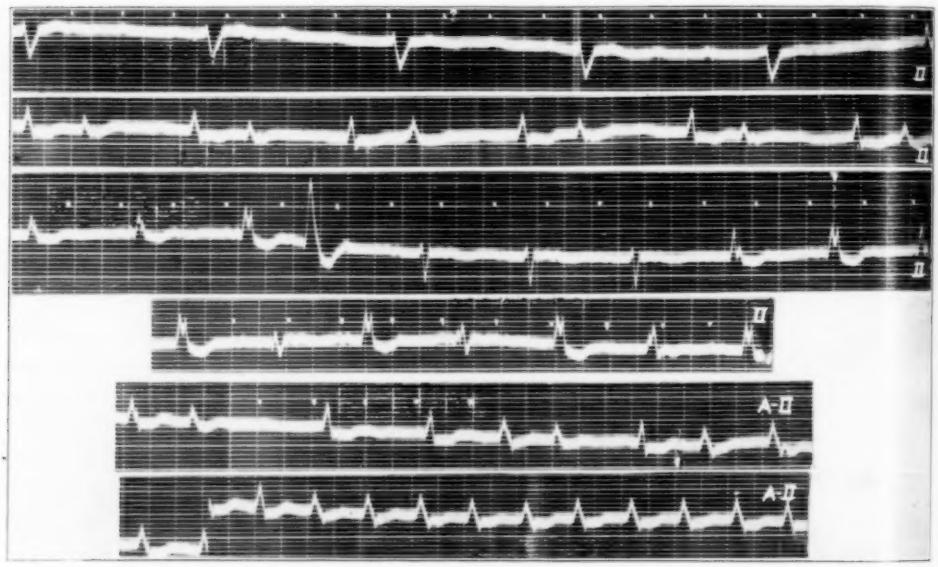

Fig. 7 (Case 3).—September 20, 4 p. m., three hours after the administration of 19 c.c. of tincture of digitalis; all strips in Lead II, the last two strips constituting a continuous record. The position of the P waves is indicated by markers.

patient's heart went into tachycardia, rate 160. The tachycardia persisted, with the rate dropping to 130, until the patient died suddenly, five hours after the administration of a massive dose of digitalis.

The necropsy report stated that the heart weighed 600 gm. (free of blood). There were ecchymotic spots along the left descending coronary branch; also, a few pericardial hemorrhages over the epicardium of the left ventricle; very few over the right ventricle. Considerable coronary sclerosis was present. The diagnosis was chronic diffuse nephritis (contracted kidney); arteriosclerosis, general; hypertrophy and dilatation of the heart, and subepicardial hemorrhages.

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6. There is nothing in the record to show that the diagnosis of pulsus alternans was verified.

Electrocardiograms were made as follows: (*a*) one day after admission; (*b*) seven days after admission, one and one half hours before the administration of the massive dose of 19 c.c. of tincture of digitalis, and (*c*) three hours after the administration of the digitalis.

Figure 6 (upper part) shows portions of the record made on the day after admission. The three leads are shown. The right hand part of the figure shows frequent extrasystoles which, in places, produce a bigeminy. The left hand part of the figure shows portions of the record in which extrasystoles do not occur. In the record made seven days later (Fig. 6, lower part) extrasystoles occur less frequently.

Figures 7 and 8 show portions of the record obtained three hours after the administration of the dose of 19 c.c. of tincture of digitalis. All the curves shown in Figure 7 were taken in Lead II. The first strip of this figure shows an auricular rate of 150 a minute with an independent ventricular rate of 43. The type of the ventricular complexes is different from that previously recorded. The auricular waves are quite small, a change which frequently occurs after

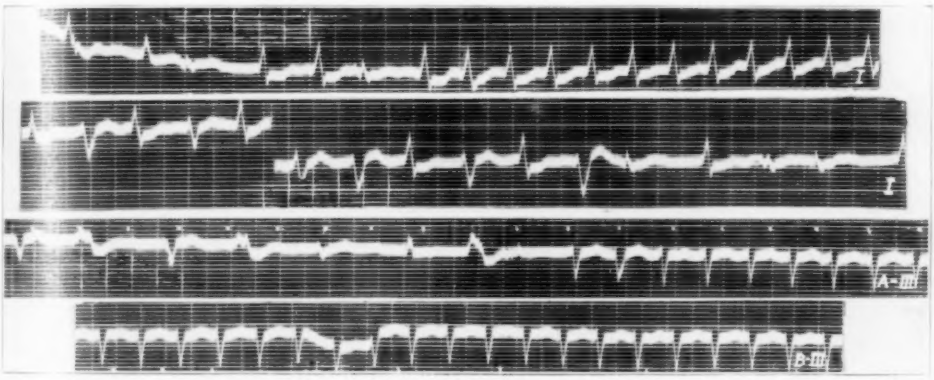

Fig. 8 (Case 3).—September 20, 4 p. m., three hours after the administration of 19 c.c. of tincture of digitalis; first and second strips, portions of Lead I; third and fourth strips, a continuous record in Lead III. The probable positions of the P waves are indicated by markers.

digitalization. Their position is indicated by markers. The second strip shows a pairing of the ventricular complexes, the shapes of both components of the pairs being similar to those which were seen the day after admission. The pairing, however, is more persistent in Figure 7, and the ventricular rate is faster. The third strip shows the auricular rate still about 150. The predominant ventricular rate is 80. In this and in the fourth strip, the shape of the ventricular complexes undergoes many changes.

The fifth and sixth strips are continuous. The latter part shows a tachycardia whose ventricular rate is 150. The beginning of this tachycardia (fifth strip) is marked by an irregularity, the exact type of which is somewhat open to question. The fact, however, that the rate of the paroxysm, after it is established, is that of the usual auricular rate, i. e., 150, would indicate its auricular origin. Auricular waves, however, cannot be clearly distinguished either in this paroxysm or in that part of the record which immediately precedes it.

Other records of tachycardia are shown in Figure 8. The first and second strips are from Lead I. The third and fourth strips constitute a continuous

record from Lead III. The first strip shows the onset of a paroxysm. The auricular mechanism is difficult to determine in this portion of the record. The rate of the ventricular complexes is 180 a minute. This is about the same as the rate at the beginning of the paroxysm whose onset is shown in the third strip, and which is probably ventricular in origin. The rate of the last mentioned paroxysm, after it is well established, is 200 a minute.

The record immediately preceding the onset of the latter paroxysm is of great interest. The small auricular complexes can be distinguished occurring at the rate that has been noted in other portions of the record, i. e., 150 a minute. The first five ventricular complexes exhibit an alternation in the direction of deflection and are of the general types indicative of interference with conduction through the right and left bundle branches. The tendency to pairing, however, would suggest that the second and fourth complexes are produced by extrasystoles which arise in the right ventricle.

A similar difficulty arises in the attempt to interpret the second strip. The complexes in this show, for the most part, an alternation in the direction of deflection. This portion of the record is quite similar to the record in the first of Schwensen's cases. The auricular mechanism in Schwensen's case, however, was normal, while the auricular mechanism in the second strip of Figure 8 is somewhat open to question. There are, however, what look like traces of small P waves occurring at the rate of about 150. The time interval between the ventricular complexes is not constant. The total rate of the ventricle for the first two thirds of this strip is 137.

One interpretation of this record that suggests itself is that the upwardly deflected complexes are premature contractions whose point of origin is in the left ventricle. In favor of this explanation is the fact that the paroxysm in the first strip is composed of complexes of similar shape, and also that the time interval between one of these beats and the beat immediately preceding it is of shorter length than the interval following it. Under this interpretation, the downwardly deflected complexes are either the "normal" ventricular beats or they also are extrasystoles. If the former, they are suggestive of delayed conduction through the left bundle branch; if the latter, they arise in the right ventricle. Another suggested explanation of these complexes is that they record a paroxysm of tachycardia whose point of origin is in the bundle at or just above its bifurcation, conduction being delayed alternately through the right and left branches. A complete explanation of these complexes is difficult to reach, but occurring as they do in close association with other mechanisms which are known to result from digitalis, the conclusion that they also are due to its action would appear clearly indicated.

COMMENT

The tachycardia which is the especial subject of this study, and which is recorded in Cases 1 and 2, presents certain features which differentiate it from that just described. It occurred in both instances, as well as in the published cases to which reference has been made, in the presence of auricular fibrillation. It is rhythmic. In the case in which a number of records were obtained (Case 2), it is closely associated with accurate coupling. This association demands special comment. No adequate explanation of coupling has been reached, but it is well known that the best examples of it occur in patients with auricular fibrillation under full digitalis therapy. Lewis suggests that coupling may be

caused by reentrant beats, and he and his co-workers [7] mention the possibility that instances in which a rapid and almost regular rhythm seems to emanate from the ventricle also may be due to reentrant beats. The most beautiful examples of digitalis coupling show an alternation in the direction of the complexes that constitute the couple, and these complexes, furthermore, exhibit, in general, shapes that are characteristic of defective conduction first through one branch of the atrioventricular bundle and then through the other.

It is frequently impossible to determine whether abnormal ventricular complexes represent aberrant beats or extraventricular systoles. Variations in the shape of ventricular complexes may be due either to changing intraventricular conduction or to changes in the points of origin of the beats. In cases that exhibit independent ventricular rhythm, the difficulty in determining which of these factors is responsible for changes in the ventricular complexes is enhanced. An explanation of the alternating tachycardia shown in these cases and in the cases reported by Schwensen, by Felberbaum and by Reid, which rests on either of the foregoing possibilities, therefore, must at present be open to question. Certain facts, however, suggest that an alternate variation in conduction through some portion of the right and left branches of the atrioventricular bundle rather than the occurrence of extrasystoles at multiple foci is responsible for the alternation in direction of the ventricular complexes of this tachycardia. The *exact rhythmicity of the complexes would be difficult to explain except on the basis of their origin at only one focus.* On the other hand, there is abundant evidence that digitalis does prolong conduction through the bundle branches as well as through the main stem. In one of my cases [2] which showed, as a toxic effect of digitalis, auricular tachycardia and aberrant ventricular complexes, there were short portions of the curve which showed an alternation in the direction of the aberrant complexes associated with shapes of the latter that were indicative of defect in conduction first through one branch and then through the other.

If, however, this unusual mechanism is indeed due to alternate interference with conduction through the bundle branches, it might appear that this interference, if high in the branches, must cause, not a mere delay in the conduction of impulses, but an absolute blocking of them. Otherwise, it would be difficult to explain how that branch which had just experienced difficulty in conducting an impulse could recover in time to transmit the succeeding impulse with even more facility than the opposite branch which had just showed no evidence of impairment.

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7. Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observations Upon the Action of Certain Drugs Upon Fibrillation of the Auricles, Heart 9:207 (April) 1922.

But these complexes do not exhibit the exact shapes that are usually attributed to complete bundle branch block. A possible escape from the dilemma is suggested in a recent report by Carter and Dieuaide [8] of the recurrence of complete atrioventricular block in a patient who showed normal atrioventricular conduction between attacks. These authors suggest that there is normally a large reserve in the conducting capacity of the atrioventricular bundle, and that a few fibers may transmit impulses without delay even though the bulk of the bundle may have suffered serious impairment. If this is true of the main stem, it may apply also to the bundle branches. Under this conception, the alternating tachycardia might be explained as follows: Digitalis intoxication results in a tachycardia which originates at or near the bifurcation of the main stem of the bundle. The action of the drug has also impaired to a considerable extent the conductivity of the bundle branches. An impulse is then transmitted over one (the right) branch but finds the other (the left), for the most part, unable, at the moment, to transmit it. A small strand in the impaired left branch, however, does transmit the impulse, but at a slower rate. This gives the picture of defective (left) branch conduction. The next rhythmic impulse finds the bulk of the left branch restored and ready for conduction, but the bulk of the right branch has not recovered, and so fails to transmit the impulse. A small strand in the right branch, however, having been less impaired by digitalis, is able to transmit the impulse but at reduced speed. This produces the picture of defective right branch conduction. The bulk of the tissues of the righ branch is then ready for the succeeding beat, but the main part of the left branch is not, and so on with successive rhythmic impulses.

The question cannot be settled merely by an inspection of records. It would, perhaps, be impossible to say whether the complexes in the latter part of the last strip of Figure 5 are aberrant, or whether they represent impulses which arise at different foci. The sixth and seventh complexes from the end alternate in direction and are fairly typical of those composing the long, regular paroxysms. On both sides of this pair the complexes change in shape. There is little to strengthen either interpretation of the cause of these changes. Digitalis is known to produce extrasystoles. It is known to increase rhythmicity.[2] It is also known to depress intraventricular conduction.[7] Both extrasystoles and aberrant complexes, doubtless, occur in many cases of severe digitalis intoxication, and it is in just such cases that independent ventricular tachycardias occur.[9]

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8. Carter, E. P., and Dieuaide, F. R.: Recurrent Complete Heart Block with Normal Conduction Between Attacks, Bull. Johns Hopkins Hosp. **34**:401 (Dec.) 1923.

9. Luten (Footnote 2). Schwensen (Footnote 3). Reid (Footnote 5).

The alternating tachycardia in question may be the expression of some sort of circulating mechanism in the ventricle. And just as the speed of transmission of impulses and the duration of the refractory phase may influence the type of circus movement in the auricle, so it may be that these factors cause further changes in such a ventricular mechanism and that, in this manner, ventricular fibrillation is produced. Experimental studies along these lines may explain the mechanism by which digitalis produces this peculiar tachycardia and by which it may possibly be shown that the latter ends in ventricular fibrillation. When the exact nature of digitalis coupling is explained, it seems probable that the key to the explanation of this alternating tachycardia will have been found.

519 University Club Building.

THE PATHOGENESIS OF TETANY

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Tetany may be defined as a condition of peripheral nervous hyperexcitability, characterized by intermittent spasms of the extremities, without loss of consciousness.

The first reference in the literature to tetany is attributed to Clarke (1815). Other names, particularly those of Kellie, Steinheim and Dansie, are associated with the earlier descriptions of the condition. The title "tetany" we owe to Corvisart.

Tetany can scarcely be regarded as a distinct clinical disease but rather as a syndrome which may occur under a number of widely differing circumstances. A proper understanding of the nature of this syndrome necessitates a close examination of the various etiologic conditions. Lacking a more accurate classification, the tetanies are usually studied under one of the following divisions:

1. Tetania parathyreopriva.
2. Traumatic tetany.
3. The idiopathic tetany of workmen.
4. The tetany of gastro-intestinal disorders.
5. Infantile tetany or spasmophilia.
6. Maternity tetany.
7. Guanidin tetany.
8. The tetany of forced respiration.
9. The tetany of nervous diseases.
10. The tetany of alkalosis and acidosis.
11. The tetany of intoxications, infections, and "overexertion."

Each of these varieties demands closer examination.

1. TETANIA PARATHYREOPRIVA

This is due to removal of the parathyroid glands. This class also includes the cases of so-called tetania strumipriva, or the tetany complicating goiter operations.

The earlier thyroid surgeons (Schiff, Wagner, Colzi, Sanquirico, and Canalis, Horsley, Weiss, Kocher, Billroth, Reverdin and v. Eiselberg) were perfectly familiar with the train of convulsive symptoms which often followed the complete removal of goiter, although they did not appreciate its significance. The existence of the internal parathyroids had been recognized by anatomists since their discovery by Sandström in 1880, but it was not until Nicolas, in 1893, had described the second or external pair of parathyroids that experiments in animal removal were seriously undertaken. Rouxeau (1897) and Vassale and

Generali (1900) were among the first to extirpate all four parathyroids, and in the great majority of cases the animals died with the convulsive manifestations known to the thyroid surgeons as tetany. Necropsy revealed no evidence of sepsis, hemorrhage or undue trauma. Further experiments were performed by Biedl, Leischner, Lusena, Cristiani, Alquier, Welsh, Edmunds, Gozzi and many others, all demonstrating clearly the association of the resulting symptoms with the tetany that had been observed to follow goiter operations. The postoperative results were not entirely uniform however; although the majority of animals died as a result of parathyroidectomy, nevertheless there were survivors. It was gradually realized that certain other factors influenced the severity of the symptoms.

Age.—Young animals were found to be more susceptible to the effects of parathyroidectomy than adults (Berkeley and Beebe, Marine, Simpson).

Type of Animal.—Carnivora most readily developed tetany: herbivora least of all. Ominvora occupied an intermediate position.

Pregnancy.—The operation results were severest in pregnant animals (Morse, Carlson).

Heredity.—The offspring of parathyroidectomized animals were particularly susceptible (McCarrison).

Diet.—Feeding on flesh or meat extracts usually aggravated the symptoms, whilst the tetany could sometimes be kept in abeyance by a milk diet (Berkeley and Beebe, Marine, Morse, Paton and Findlay). Dragstedt, Phillips and Sudan (1923) find that feeding with putrid meat produced more violent manifestation than a fresh meat diet.

Coexistence of Rickets.—Rachitic animals are very susceptible to parathyroidectomy (Morel, Paton and Findlay). Animals that survived the acute phase passed into a state of "latent tetany" characterized by emaciation, weakness and numerous trophic disturbances such as falling out of the hair, osteoporosis, enamel changes and cataract formation. Acute convulsive manifestations were readily precipitated by even the slightest stimuli, such as the advent of pregnancy or the estrum, the injection of tuberculin or of placental extract.

2. TRAUMATIC TETANY

This group comprises those cases of tetany where actual damage to the parathyroid glands has been known to occur. Thus Cordier reported fatal tetany in a man, aged 41; necropsy demonstrated a large cervical hematoma which had destroyed all the available parathyroid tissue. Proescher and Diller have recorded fatal tetany occurring in a young man eight days after a severe blow. Postmortem examination revealed numerous recent hemorrhages into the parathyroids, which

appeared to be hypoplastic. Cases of sudden death among infants occasionally occur as the result of traumatic hemorrhage into the parathyroids. Three such cases have been recorded by Crosser.

3. IDIOPATHIC TETANY

This is the name applied to a particular form of tetany, rare in this country but not uncommon in certain parts of the continent. It also goes under the names of tetany of workmen, or epidemic endemic tetany.

Etiology.—There are many points of very great interest in the etiology of this condition.

Sex: Men are much more often affected than women. Out of 418 cases collected by v. Frankl-Hochwart, 399 occurred in men and only nineteen in women.

The age incidence is that of early adult life (from 15 to 25).

Place: Tetany is endemic in Vienna and Heidelberg, but becomes epidemic in character about every tenth year. The other parts of Austria and Germany are comparatively free from the disease. Tetany occurs also in Russia and other parts of the Continent but is rare in Great Britain and America. In India, tetany is endemic in certain valleys in the northern provinces, often corresponding with the goiter districts.

Hereditary appears to contribute to the production of tetany, and several members of a family may be simultaneously attacked.

Occupation, for some obscure reason, constitutes an important etiologic factor. A large proportion of the men affected are tailors and shoemakers by trade, whilst among the women, seamstresses are most frequently affected. Out of 528 cases collected by v. Frankl-Hochwart, 223 were shoemakers and 117 were tailors. In the Petrograd outbreaks of tetany, metalworkers are particularly liable to the disease (Voss).

Seasonal incidence: A very large percentage of the cases occur in the spring, February, March and April being sometimes spoken of as "the tetany months."

The prognosis is good in these cases, the average length of the illness being from two to three weeks. Death is extremely rare.

4. THE TETANY OF GASTRO-INTESTINAL DISORDERS

There are two main varieties of alimentary disorders which are apt to be complicated by tetany: (1) gastric dilatation; (2) colonic inflammations (chronic diarrhea, worms, etc.).

Gastric Tetany.—The commonest etiologic factors in this condition are persistent vomiting and dilatation of the stomach.

Tetany is a rare complication in gastric diseases and probably never occurs except in patients who were in a state of latent tetany. In such persons, acute symptoms are brought on by quite trivial stimuli; thus

they may arise during the operation of gastric lavage or even after simple percussion over the epigastrium (Gerlardt).

During infancy, gastric tetany occasionally arises in the course of such diseases as cyclic vomiting, congenital duodenal stricture, or hypertrophic stenosis of the pylorus.

Experiments were made by MacCullum, Lintz, Vermilye, Leggett and Boas on the operative occlusion of the pylorus in dogs. Tetany appeared after a variable interval. There was an increase in the alkali reserve of the blood. The experiments were repeated the following year by Hastings, Murray and Murray, with the production of tetany in every case. The blood showed an increase both in the alkali reserve and in the calcium content.

Colonic Tetany.—This is usually preceded by a prolonged spell of diarrhea. In adults, tetany has been reported as a complication in such diseases as sprue (Bassett-Smith, Dorvain, Barach, and Murray) or chronic dysentery (Savy and Langeron). Blumgart reports two cases of chronic diarrhea, anemia, and acidosis, in which tetany was a terminal feature. Tetany may also occur in infections with a tapeworm (Riegil, Greenfield).

In infants, celiac disease or tuberculosis of the bowel occasionally give rise to tetany. Langmead (from 1906 to 1909) collected nine cases of tetany in children, aged from 2½ to 8 years, associated with dilated colon, chronic diarrhea, and the passage of offensive, porridge-like stools. Possibly these were actually cases of celiac disease.

5. INFANTILE TETANY (SPASMOPHILIA)

During the first three years of life many infants are characterized by hyperexcitability of the peripheral nervous system and by muscular hypertonus. From time to time these children may be seized with generalized convulsions or attacks of laryngeal spasm. Such children were spoken of by Finkelstein as exhibiting the "spasmophil diathesis." Occasionally attacks occur which are indistinguishable from those of adult tetany. Such attacks usually show a definite seasonal incidence, and are closely associated with rickets and gastro-intestinal disorders.

In studying a series of cases of infantile tetany, two main groups may be detected.

(*a*) A larger group of cases almost always occurring in improperly fed infants. Rickets is very frequently present, and the tetany is usually preceded by an attack of gastro-enteritis. (*b*) Cases of tetany of other causation, occurring in infants. Such instances are those of nephritis tetany, the tetany of chronic diarrhea, etc. The children are usually a little older, and there is no definite etiologic association with rickets. These cases form but a small group and should be considered apart.

Male infants with tetany slightly outnumber the female, and the poorer classes are more often affected than the well-to-do. There is a definite seasonal incidence, the majority of all cases occurring in the months of February, March and April. Scarcely any cases are met with during the summer months. Dr. John Thomson remarked on the prevalence of tetany when cold winds were blowing.

Heredity certainly takes a part in the etiology; the mothers of many spasmophilic infants themselves show signs suggesting a condition of latent tetany.

Inquiry into the diet elicits many points of interest.

1. Tetany is very rare in breast-fed infants.

2. Tetany usually arises in babies fed on one of the proprietary milk preparations; less frequently it is seen in infants fed on cow's milk mixtures. Finkelstein set out to determine which constituent of milk was responsible for the production of tetany. By the addition of the various components of milk to the dietary he found that neither the fat, sugar nor protein was responsible, but that one or all of the inorganic salts was the causative factor. Brown and Fletcher found that infants fed on a high carbohydrate dietary were liable to develop tetany, provided the proprietary article had been subjected to a high temperature in the course of its manufacture.

The association of rickets with tetany is particularly striking, being first pointed out by Sir William Jenner. In Kirchgasser's series of 263 cases, rickets was present in 79.8 per cent.; Escherich puts the proportion as high as 95 per cent. Associated with attacks of tetany, laryngospasm or even generalized convulsions may occur simultaneously. The actual precipitating cause of tetany in rachitic children is usually an attack of gastro-enteritis. Acute specific fevers, bronchopneumonia, streptococcal sore throats, teething or worms will also act as a source of irritation sufficient to translate latent spasmophilia into actual tetany.

6. MATERNITY TETANY

Tetany may arise in the course of pregnancy (tetania gravidarum) or during lactation (tetania lactarium). It is uncommon in this country, but is not rare in Vienna and other localities where tetany is endemic. The patient during the latter half of pregnancy is much more liable to tetany, especially during the sixth, seventh and eighth months. The actual onset may even date from the commencement of uterine contractions (Neumann).

7. GUANIDIN TETANY

Guanidin is a nitrogenous basic substance of highly toxic properties, occurring in minute traces in the liver, muscles, serum and urine, and is probably excreted either as creatinin or urea. Convulsive manifestations have been known to follow injection of the substance (Gergens and Baumann, 1876; Putzey and Swaen, 1876; Fuhner, 1906).

Paton and Findlay (1916) carried out a series of injection experiments in animals, with the production in every case of symptoms indistinguishable from those of parathyroid tetany. One may reproduce here a summary of their findings:

1. Small doses of guanidin excite the spinal cord while large doses depress it.

2. Guanidin tetany is relieved by calcium.

3. Latent tetany can be precipitated by guanidin in doses insufficient to cause symptoms in normal dogs.

4. Guanidin increases the electrical excitability of the peripheral nerves.

5. There is an optimum concentration for the action on the peripheral nerves, while the action on the central nervous system is directly proportional to the dose.

6. Parathyroid tetany resembles guanidin tetany in all particulars (spasticity, tremors, increased electrical excitability, loss of balance, etc.).

8. TETANY OF FORCED RESPIRATION

Tetany arising in the course of alterations in the respiratory rhythm (light anesthesia, tachypnea, etc.) has been noted by Vernon (1909), Yandell Henderson (1909), Hill and Flack (1910), Stein (1916) and Collip and Backus (1920). Barker and Sprunt (1921) reported a case of hysterical polypnea followed by tetany occurring as a sequel to encephalitis lethargica. The most interesting contribution, however, has come from America; Grant and Goldman (1920) produced transitory attacks of tetany in normal persons by the process of "overventilation of the lungs." The subject, lying on his back, breathed as deeply as possible, slowly and regularly. In every case, tetany developed after an interval of from fifteen minutes to an hour.

9. THE TETANY OF ALKALOSIS

There are many cases on record of tetany arising after the therapeutic administration of large doses of alkalis. Blum produced spasms in diabetic patients by the intravenous administration of alkalis. Howland and Marriott recorded other cases among infants. Horrop produced tetany in an adult with mercurial poisoning by the administration of bicarbonate of soda. Healy recorded six instances of tetany developing in women after the rectal administration of 80 gm. of sodium bicarbonate in mistake for simple enemas. Four of the patients died but the other two recovered after vigorous calcium medication. Another case of tetany in alkalosis is reported by Tiletson and Underhill.

10. THE TETANY OF ACIDOSIS

Although cases of actual tetany are rare manifestations in acidosis, an increase in the electrical excitability of peripheral nerves is not

uncommon in bronchopneumonia, pertussis, nephritis, rickets and other diseases of infancy associated with an alkalipenia. It is possible that the tetany which has been observed to follow the administration of serum is actually an example of the tetany of acidosis.

11. THE TETANY OF NERVOUS DISEASES

Tetany has been observed as a rare complication in certain nervous disorders, in particular, cerebellopontine angle tumors, syringomyelia, meningitis and Friedreich's ataxia.

12. THE TETANY OF INFECTIONS AND INTOXICATIONS

Occasionally tetany arises in the course of an acute specific fever, especially in those districts where idiopathic tetany is endemic. Typhoid in particular is apt to be complicated by tetany, while it is not unknown in the course of influenza, pneumonia, scarlet fever or cholera. The various intoxications, lead, mercury, chloroform, alcohol, morphin, male fern, spermin, and phosphorus have all been known to give rise to tetany.

13. THE TETANY OF OVEREXERTION

James Collier has recorded a case of a girl guide who constantly developed typical tetanic spasms after she had performed long distance marches.

CLINICAL FEATURES OF TETANY

With a few relatively unimportant exceptions, the symptomatology of the various types of tetany is remarkably similar. A brief description is advisable of the phenomena common to these varieties. The brunt of the morbid process falls on the nervous system, the peripheral neurones suffering more than the higher centers. The phenomena may be conveniently studied under three headings: (1) motor; (2) sensory; (3) sympathetic or vasomotor.

The chief motor manifestations consist of intermittent tonic spasms of the extremities, without any loss of consciousness. The hands and feet take up characteristic postures (accoucheur's hand; carpopedal spasm). In animals there are in addition muscle fibrillation, hypertonus, choreiform macrokinetic movements of the limbs, and "intention spasms." The peripheral nerves are markedly hyperexcitable and respond with the greatest readiness to mechanical and electrical stimuli.

Sensory manifestations are rarer and include subjective sensations of pain, numbness, tingling, etc. There may be an actual electrical hyperexcitability of the sensory nerves (Hoffmann) or the nerves of special sense (Chvostek, Jr.). Kashida has pointed out that the application of hot or cold objects may elicit an increased sensory motor reaction.

Sympathetic upset is expressed by involvement of the unstriped musculature and by vasomotor derangements. Thus one may find spasm of the esophagus and larynx, and of the pyloric, anal or pupillary

sphincters; of the diaphragm (Bechterew); or of the bronchi. Alterations may occur in the respiratory mechanism causing apnea or polypnea. Tachycardia is common, especially in dogs, and death has been said to occur from "tetany of the heart." Among the vasomotor upsets one may include lachrymation, polyuria, salivation, intermittent hydrarthroses, edema, mydriasis, hyperhidrosis and dermographism. Arterial spasms may give rise to a condition resembling Raynaud's disease, or even to transient attacks of amaurosis. Falta states that there is an increased susceptibility to injections of pilocarpin and epinephrin.

METABOLISM IN TETANY

All clinical varieties of tetany are accompanied by grave metabolic changes which, although differing in certain details, present on the whole a marked uniformity. The most constant and striking alterations in the majority of cases of tetany occur in the calcium metabolism. There is first an increased excretion of lime and a reduction in the $\frac{\text{urinary calcium}}{\text{fecal calcium}}$ ratio. Secondly there is a depletion in the calcium reserve of the body. Erdheim remarked on enamel changes rapidly following parathyroidectomy, causing the teeth to decay and snap off; fractures also healed slowly and with imperfect callus; Leopold and v. Reuss found a quantitative diminution in the lime content of the bones, whilst Iselin reported osteoporotic skeletal changes. The proportion of lime falls in muscles (Underhill and Blatherwick) and also in the brain (MacCullum and Voegtlin, Edmunds, Quest and Czerny). A reduction in the serum calcium content is a very frequent phenomenon; Howland and Marriott maintain that tetany will not arise until the calcium level falls from the normal (10 mg. per cent.) to 5 mg. Cruickshank (1923) states that there is a relative increase in the amount of diffusible calcium, with a reduction in the total quantity. The amount of calcium in the cerebrospinal fluid is normally very constant, but in tetany it may be reduced to mere traces (Critchley and O'Flynn). Although the reduction in the serum calcium content is usual, there may, however, be actually a slight increase in certain varieties of experimental tetany (e. g., after forced respiration, or the ligature of the pylorus in dogs). The whole picture of the calcium metabolism may be crystallized in the term "negative calcium balance."

Changes may occur in the metabolism of other inorganic compounds; thus a phosphorus retention is common (Greenwald, Salvesen); sodium and potassium are often retained and the excretion of sulphur may be increased (Greenwald). Changes in the magnesium content are not constant (Howland and Marriott). Loeb and Matthews emphasize the importance of the balance between the metallic salts in

tetany; in their opinion the characteristic change lies in the increase in the ratio $\frac{\text{sodium} + \text{potassium}}{\text{calcium} + \text{magnesium}}$ in the blood (Kramer, Tisdall and Howland).

The nature of the acid base upset in tetany is controversial, as both acidosis and alkalosis have been observed. In tetania parathyreopriva, Morse, Cordier, Togawa, Salvesen and Greenwald have reported states of acidosis, whilst McCann stated that an alkalosis is present. Wilson, Stearns and Thurlow state that there is a condition of alkalosis rapidly followed by acidosis. Howland and Marriott found a normal alkali reserve. Alkalosis was constant in the tetany of forced respiration.

The nitrogen metabolism is characterized by:

1. An increased excretion of nitrogen.
2. An increased $\frac{\text{urea N}}{\text{total N}}$ ratio in urine.
3. An increased ammonia ratio.
4. An occasional rise in the ammonia content of the blood.
5. Creatinuria and an increased output of creatinin. (In guanidin tetany there is also an increase in the creatin content of the muscles [Wishart].)
6. The appearance in the blood stream of certain protein derivatives normally excreted as urea and which are highly toxic bodies. Chief among these are guanidin and methylguanidin. The origin of these bodies is uncertain and cyanamid (Koch), arginin, creatin and lecithin (Paton) have been cited as the possible precursors. The urinary output of these bodies is also greatly increased, and there is a reduction in the amount of guanidin normally present in muscle.

There are but few references in the literature to the metabolism of the carbohydrates. Watanabe reported a lowering of the blood sugar level in experimental tetany and G. A. Clark has found a similar condition in guanidin tetany.

The utilization of fats by the organism appears to be diminished (Underhill, Tilestone and Bogert).

The pathogenesis of tetany is still a matter for much speculation and many theories have been formulated to explain its clinical and pathologic features. The earlier observers regarded tetany as a manifestation of acute rheumatism; later it was spoken of as a form of intermittent tetanus. Today there are three main hypotheses which demand attention, and they may be spoken of as the calcium privation theory, the endocrine theory, and the theory of toxic origin. Each one requires closer study.

THE CALCIUM PRIVATION THEORY

This theory, formulated by MacCallum and Voegtlin in 1908, has received wide recognition, being based on a large number of observations, experimental, clinical, metabolic, pathologic and therapeutic. Thus Sabbatani (1901) by applying a solution of lime salts to rabbits' convolutions, was able to reduce the excitability; conversely, the applica-

tion of calcium precipitating solutions (e. g., oxalates) caused a hyperexcitability of the cerebral cortex. Loeb (1902) showed that the injection of oxalates or citrates into animals produced muscular twitchings. MacCallum, Lambert and Vogel (1914) perfused an amputated limb with calcium freed blood, with the production of peripheral nervous hyperexcitability. On the clinical side, tetany is known to occur frequently in conditions characterized by a calcium drain such as pregnancy, lactation, rickets and occasionally osteomalacia. Biochemical examination shows that the calcium content of the serum and cerebrospinal fluid is very frequently reduced while the output is increased; at the same time there is an actual diminution in the amount of calcium present in the brain, muscles, bones and teeth. The therapuetic value of intravenous calcium salts in tetany is unquestionable although the effect wears off after twenty-four hours. Bergheim, Stewart and Hawk (1914) and Salvesen (1922) have shown that the manifestations of tetania parathyreopriva may be kept in abeyance by feeding the animals on a high calcium diet for some time before operation.

These observations are all of striking interest and merit close consideration, but a number of opposing facts may be cited which combine to render this present theory untenable. Thus whilst conditions of increased lime excretion are undoubtedly liable to be followed by tetany, nevertheless tetany even more frequently occurs without any such etiologic factor being demonstrable. Secondly, the interpretation of the results of blood calcium analyses requires consideration; can the low figure in tetany be due to a mere mechanical dilution of the blood by a condition of hydremic plethora, as in some cases of nephritis? Or again, may not the low calcium figure be the result rather than the cause of the tetany? Thus in cases of rapidly produced experimental tetany (as in forced respiration or ligature of the pylorus) there is no reduction in the serum calcium. Moreover, in diabetes and other diseases the calcium level may fall considerably without tetany resulting. The figures may also be lowered experimentally by the injection of phosphates, or copious bleeding followed by saline infusions, and no tetany appears. With reference to the benefit from calcium medication, it must be remembered that calcium is not alone in its therapeutic effect; thus barium and magnesium salts are also efficacious; Canestro has derived benefit from injecting strontium compounds, whilst Frouin found lanthanum and thorium of value. Saline transfusions may also be beneficial (MacCallum and Voegtlin; Joseph and Meltzer). Most important of all, Paton and Findlay, Cruickshank and many others have shown that mere bloodletting alone will definitely improve symptoms in tetany.

THE PARATHYROID THEORY OF TETANY

The striking similarity in clinical and metabolic features of the tetanies to the manifestations following parathyroid removal tempt one

to formulate a common pathogenesis. The unitary conception of Pineles' attempts to place all varieties of tetany on a common pathologic basis, namely, parathyroid insufficiency. Thus the idiopathic tetany of Vienna is said to be due to an acute specific infection picking out the parathyroid glands; gastric and colonic tetany arise from the action of bowel toxins on an unstable parathyroid system; maternity tetany is due to a physiologic parathyroid upset aggravated by a severe calcium drain; spasmophilia is due to a lesion of the glands in infancy and Erdheim and others have found hemorrhages into the glands at necropsy; guanidin tetany is due to lack of the ferment arginase, which is present in the parathyroids and which converts guanidin into urea.

This hypothesis, however, is deplorably barren in chemical, histologic or clinical evidence. The significance of necropsy parathyroid hemorrhages is very doubtful; they are commonly found in postmortem examination of patients dying in convulsive or comatose states, such as cerebral tumor, uremia, etc. Moreover, histologic evidence has been negative in the great majority of necropsies on cases of tetany. The hypothesis of the toxic action of bowel amins in the production of gastric and colonic tetany is unsupported by the work of Muller, Strauss, Gumprecht, Ewald and Jacobsohn, Albu and others, who have searched in vain for any such poisonous bodies. Tetany, however, is conspicuously rare in those cases which are essentially characterized by fecal stasis and toxin absorption, namely, Hirschsprung's disease, splanchnoptosis, and chronic intestinal obstruction.

The evidence of parathyroid instability during pregnancy is extremely meager, and there are many other gross metabolic changes apart from those occurring in the calcium balance. It seems extremely improbable that the absence of four such minute bodies as the parathyroids should deplete the organism of its supply of arginase when the spleen is known to contain large amounts of this ferment. The tetany of forced respiration is scarcely explicable by this theory, for it is difficult to conceive a temporary parathyroid insufficiency occurring in a normal person and persisting only for an hour. Lastly, it may be pointed out that although parathyroid grafting is occasionally of value in the tetany following goiter operations, the treatment of tetany by parathyroid extract is futile.

THE THYROIDAL THEORY

In many respects the thyroid and parathyroid glands are opposed in function, and it is conceivable therefore that the symptoms of parathyroid tetany may be due to an uncompensated thyroidal effect (Rudinger). McCarrison has shown that the geographic distribution of idiopathic tetany corresponds closely with that of endemic goiter. Such an hypothesis, however, fails to explain why tetany should occur

when both thyroid and parathyroids are simultaneously removed. The clinical expression of thyroid overactivity, namely, exophthalmic goiter, bears but little resemblance to tetania parathyreopriva.

THE THEORY OF THYMUS OVERACTIVITY

Uhlenhuth (1917) injected salamander larvae with thymic extract and so produced tetany. At a later stage in their development, namely, after the appearance of the parathyroids, spontaneous cure resulted. Uhlenhuth thereupon suggested that the thymus and the parathyroids had mutually opposing secretions; the tetany following the removal of the latter was therefore due to the uncompensated action of the thymus.

On the other hand, Honeyman has shown that removal of the thymus and parathyroids, in mammals at least, will result in tetany. Moreover, removal of the parathyroids in the adult will still cause tetany, although the amount of active thymus tissue must be extremely small. Again, conditions giving rise to an hypertrophy of the thymus, such as may occur with lymphosarcomas, or in myasthenia gravis, are not characterized by symptoms of tetany.

THE ANOXEMIA THEORY

Morris (1923) demonstrated that the production of a state of anoxemia in animals caused a constant increase in the electrical excitability of the peripheral nerves. This artificial oxygen starvation he produced by the following methods: (*a*) by partial asphyxiation; (*b*) by lowering the surface temperature; (*c*) by producing a profound anemia; (*d*) by the administration of sublethal doses of cyanids, thus creating a nondissociable hemoglobin-oxygen combination.

In every cases, peripheral hyperexcitability (increased electrical excitability) resulted.

Clinically, conditions of anoxemia may arise in: (1) profound anemias (e. g., rickets, sprue); (2) conditions of malventilation (as in the Glasgow slums where rickets and tetany are rife); (3) pulmonary diseases, where increased electrical excitability or even tetany may occur. Bronchopneumonia and whooping cough are the best examples of this type. Morris found a kathodal opening contracture of 3 m.a. in two infants with bronchopneumonia and a kathodal opening contracture of 1.8 in a case of pertussis.

Associated with these states there may be also a reduction in the serum calcium content.

Before accepting this theory it must be remembered that bronchitis is a frequent concomitant of rickets; hence probably the associated increase in nervous excitability and lowered serum calcium in respiratory diseases. The anemia in rickets and sprue is seldom so profound

as to cause an anoxemia, while tetanic manifestations are rare in the very grave anemias. Incomplete oxidation is known to precipitate calcium in various situations; no such calcareous deposition occurs in tetany.

THE GUANIDIN THEORY

The injection of guanidin has been known to produce muscular spasms in animals since 1876, but no association was ever suggested between these phenomena and tetany until Koch in 1912 demonstrated that methylguanidin appeared in increased amounts in the urine of parathyroidectomized dogs. Burns and Sharp (1916) estimated the guanidin content of the urine and blood in normal and tetanic dogs, and found a marked increase in the latter. They then found a similar increase in the urine of spasmophilic infants. Paton and Findlay therefore commenced a series of experiments in the production of tetany by guanidin injection. They found in every case such a striking similarity in clinical and metabolic phenomena that they formulated the theory of guanidin intoxication as the cause of tetany. The function of the parathyroids they believed lay in the regulation of guanidin metabolism and the control of muscle tonus. The rôle of the calcium reserve was to render the toxins innocuous, either by direct combination or by decreasing the permeability of the tissue cells.

This hypothesis, although accounting for most of the phenomena in tetany, fails, however, in some few particulars. It does not explain the changes in the acid base equilibrium which are so prominent in tetany; neither does it explain the rapid production of tetany in normal persons by a process of overventilation of the lungs. These are both phenomena of great importance in the pathogenesis and require explanation.

PRESENT THEORY

On reviewing the facts at one's disposal concerning the etiology and metabolism of each variety of tetany, it will be noticed that only one feature is common to all, namely, an alteration of the metabolism of nitrogen. Calcium upset and disorders of the acid base equilibrium are both of frequent occurrence, but there are many cases of tetany in which no such changes are demonstrable. The present suggestion is that the precipitating cause in all types of tetany is an alteration in nitrogen metabolism leading to the appearance in the blood stream of highly toxic nitrogenous by-products which are normally excreted as urea or creatin. These toxic substances are probably guanidin or some of its derivatives. Two other factors of importance will require explanation: (1) The cause of the perverted nitrogen metabolism, (2) the rôle played by calcium.

The factors regulating the metabolism of nitrogen are extremely numerous and upset if any one of these is liable to give rise to tetany.

Whilst the exact nature of these regulating processes is unknown, many probable factors may be pointed out.

ENDOGENOUS FACTORS

Parathyroid Integrity.—The gross changes in nitrogenous equilibrium resulting from parathyroid removal suggest that an important if not the principal function of these glands is to help control the metabolism of nitrogen. In the absence of adequate compensating factors, therefore, parathyroid removal is followed by abnormal katabolic changes in the nitrogen reserve, which are manifested clinically as tetany.

Autointoxications.—Pregnancy may be regarded in many ways as a state of toxemia in which the nitrogen balance suffers. Severe perversion will lead to tetany. The gastro-intestinal varieties of tetany are also capable of a similar explanation.

H^+/OH^- Equilibrium.—Gross changes in the acid base balance naturally alter the normal nitrogen functions, and in several cases tetany results. Such may be the explanation of the tetany following massive alkali medication, the tetany of ketosis, or the administration of serum, and of forced respiration.

EXOGENOUS FACTORS

Diet.—It is possible that nitrogen metabolism is affected by an inadequate or unsuitable dietary or by the absorption of poisons from the alimentary tract: examples may be found in ergotism, intoxication by the male fern, lead, mercury, spermin, etc. A high creatin diet is another deleterious influence on the normal path of nitrogen.

Respiration.—Conditions of anoxemia or conversely a deficiency in carbon dioxid, by altering the acid base mechanism of the body, alter the ammonia reserve. This suggests an explanation for the occurrence of electrical hyperexcitability in states of partial asphyxia, and also the tetany of forced respiration.

Vitamin Deficiency.—The metabolic results of a vitamin deficient diet are extremely varied and nitrogen suffers to no small extent, as may be shown by the occurrence of acidosis. Hence possibly arise the spasmophilia of rickety infants, and the tetany occurring in sprue and celiac disease. It is not even necessary for the diet to be deficient in a vitamin; the important point is the absorption. Conditions of chronic diarrhea and persistent vomiting are essentially states of malabsorption, and it is conceivable that tetany, when arising in these diseases, is due primarily to nonassimilation of vitamins.

Acute Infections.—The epi-endemic nature of the tetany of workmen, its hereditary and familial tendencies, its seasonal incidence, its

transient and often febrile course, the frequency of recurrences, all point to an acute organismal infection. Paton and Findlay suggest that the virus selects the parathyroids the same way that mumps picks out the parotid gland.

The rôle of the calcium metabolism lies in the neutralization of circulating toxins either by direct combination to form an innocuous substance or by rendering the tissues less permeable. The circulating calcium acts as a restraining influence on the activity of the central nervous system, and in its capacity as a base helps to regulate the p_H concentration of the blood. The appearance in the circulation of toxic nitrogenous by-products will therefore deplete this reserve, causing a negative calcium balance, a hypersensitivity of the peripheral neurones, and an upset in the normal $\frac{[H^+]}{[OH^-]}$ mechanism. The administration of calcium salts, the withdrawal of blood or the dilution of the circulating poisons by saline all naturally alleviate the symptoms of tetany, and tend to break the vicious circle that has been formed.

SUMMARY

Tetany is a metabolic disorder, characterized clinically by peripheral nervous hyperexcitability and by intermittent spasms of the limbs.

It may arise either as a disease sui generis (idiopathic tetany) or as a complicating factor in the course of other morbid or physiologic states.

Tetany is essentially an intoxication by nitrogenous by-products which may appear under a great variety of conditions.

There is no evidence that parathyroid upset is the cause of the symptoms in any variety except tetania strumipriva.

The acid base mechanism and the calcium metabolism may be secondarily affected in tetany.

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CLINICAL NOTES ON THE CHANGES FOLLOWING THE ADMINISTRATION OF DIGITALIS; COMMENTS ON THE LEVOCARDIOGRAM, DEXTROCARDIOGRAM AND BICARDIOGRAM

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A lesion of a branch of the bundle of His is not as rare as is commonly supposed. It is one of the heart defects that can only be detected by means of electrocardiographic records, and because these are often difficult to secure a great many of these cases are unrecognized. One who has the opportunity of studying large numbers of heart defects with the aid of electrocardiograms is able to make this diagnosis at fairly frequent intervals.

The facts presented in this paper are based on a study of twenty-five cases seen in the last six years. For this purpose only those cases which show curves that are generally accepted as typical of this lesion have been selected, the cases showing graphic records of a less characteristic type will not be considered at the present time.

The following criteria have been used in selecting curves which are included in the present group.

1. Q-R-S interval exceeds 0.1 second.
2. Q-R-S showing a considerable amplitude.
3. Q-R-S notched in the leads of considerable amplitude.
4. T′ large and opposite in direction to the main deflection of Q-R-S.

As to the type of curve characteristic of a lesion of the right as contrasted with a lesion of the left branch of the bundle, there is still a difference of opinion.[1] The records secured from experimental animals are not constant and must be used with much caution in interpreting the lesions in man. Further, the pathologic evidence is quite conflicting. We have no new evidence to offer in the solution of this

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*Read by title before the American Society for Clinical Investigation, Atlantic City, May 5, 1924.

1. Eppinger and Rothberger: Ueber die Folgen Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**:1, 1910. Eppinger and Stoerk: Zur Klinik des Elektrokardiograms, Ztschr. f. klin. Med. **71**:157, 1910. Cohn and Lewis: The Pathology of Bundle Branch Lesions of the Heart, Proc. New York Path. Soc. **14**:207, 1914. Lewis: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc. London **207**:221, 1916. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920. Oppenheimer and Pardee: The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, Proc. Soc. Exper. Med. & Biol. **17**:177, 1920.

phase of the subject and therefore will not discuss it. For the purposes of the present paper we will use the most widely accepted interpretation, namely: (1) The main deflection of the Q-R-S group directed upward in Lead I and downward in Lead III indicating a lesion of the right branch; (2) the main deflection of the Q-R-S group directed downward in Lead I and upward in Lead III indicating a lesion of the left branch.

As a rule the history, physical signs and course of these cases have no clue in them to distinguish them from cases of chronic myocarditis with gradually advancing cardiac insufficiency. Certain patients who presented evidence of a complete auriculoventricular block, in conjunction with a defect of a branch of the bundle, have shown the bradycardia and sometimes the attacks of unconsciousness characteristic of the Adams-Stokes syndrome.

The treatment of these cases of bundle branch block has been most unsatisfactory. In a number, the administration of atropin, epinephrin and thyroxin has been carefully studied but the changes produced have been of little moment and have always been transitory. In only five of the twenty-five cases was there definite evidence of a syphilitic infection; to these, antisyphilitic treatment was administered with little if any noticeable effect on the heart. Rest, measures directed to the correction of the abnormal renal function and in some cases digitalis have seemed to be our only dependable allies.

Of the twenty-five patients, sixteen were men and nine women. Twenty were over 50 years of age when the graphic record of a bundle branch lesion was secured. Three patients were between 30 and 40 years of age, two between 40 and 50, fourteen between 50 and 60 and six between 60 and 70.

Four of these patients have disappeared from sight and the outcome is unknown. Of the remaining twenty-one, only three are living, one of these has been under observation for four years, the others for fourteen and ten months respectively. Eighteen are dead; most of them died within six months after the electrocardiographic record showing the bundle branch lesion was obtained; two of them lived for over one year, one for three and a half years.

Chart 1 shows the electrocardiographic records of three leads secured from a woman, aged 60 years, who lived for three and one half years after the diagnosis of this defect was made. The curves present all the characteristics of a lesion of the right branch of the bundle, the Q-R-S complex is of considerable amplitude, is notched and requires 0.14 second for its completion, the T′ wave is large and opposite in direction to the main deflection of Q-R-S. The principal ventricular deflection is directed upward in Lead I and downward in Lead III. This presents the type of curve most frequently encountered.

In Charts 2 and 3 curves are presented, interpreted as indicating lesions of the left branch of the bundle. A lesion of the left branch of the bundle is an exceedingly rare finding; in our series of twenty-five cases these are the only ones we have seen. A review of the literature indicates that others have observed them very rarely. The reason for the greater frequency of damage to the right bundle is not altogether clear. It has been explained by the anatomic differences in the two branches. The left branch subdivides soon after its origin from the

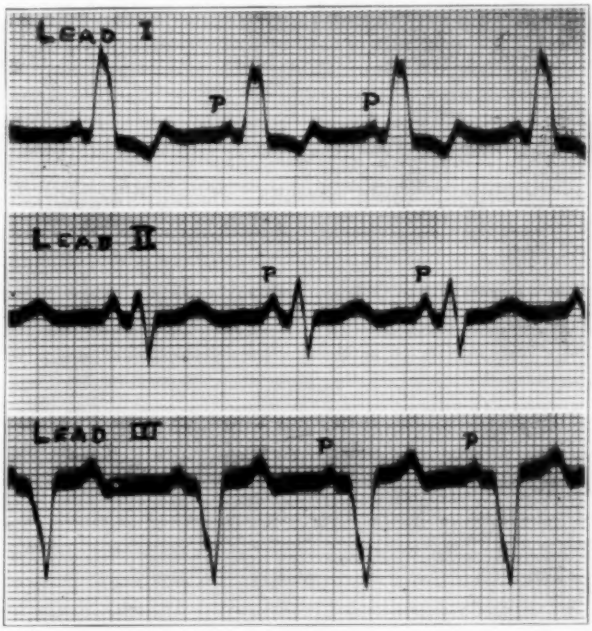

Fig. 1.—Right bundle branch block. Levocardiogram, written primarily by the left ventricle.

main stem, spreading out over the interventricular septum, while the right branch is continued as a single strand for a considerable distance. It would therefore be more easily destroyed by a single small lesion.

The records shown in Chart 2 are from a patient seen in consultation in February, 1923. He was a man, aged 47, who had been perfectly well until November, 1922. At that time he had an attack of unconsciousness and the heart was found to be irregular with a rate of 60. In December he had a second attack in which he was unconscious but the heart rate was not observed. The third attack occurred in

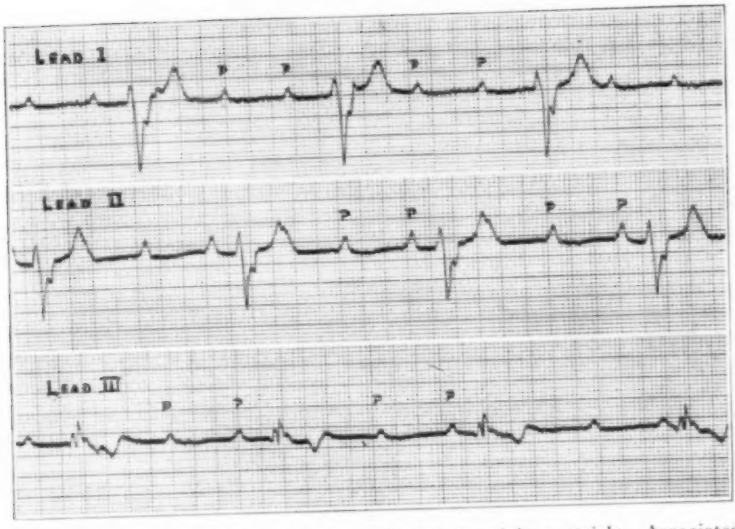

Fig. 2.—Dextrocardiogram, written primarily by right ventricle. Associated block of the bundle of His.

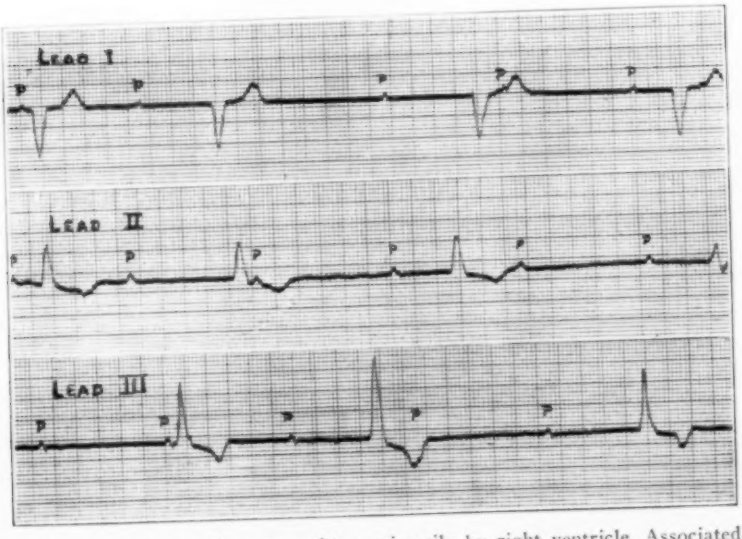

Fig. 3.—Dextrocardiogram, written primarily by right ventricle. Associated block of the bundle of His.

January, 1923, when he fell in the bathroom and was unconscious for some minutes; the heart rate was 28 and since that time has never exceeded 39 per minute. It has never been possible to discover a satisfactory explanation of the cause of the heart lesion. The heart was not enlarged and no murmurs could be detected. The effect of atropin, epinephrin and thyroxin were studied without any appreciable influence on the block. He is still living but has attacks of unconsciousness at irregular intervals.

The other patient giving a curve (Chart 3) of a lesion of the left branch of the bundle was a single man, aged 48, a traveling salesman, seen in consultation in May, 1923. He is still living. As a child he had diphtheria, and gonorrhea as a young man. There were no other illnesses. He denied any syphilitic infection, and the blood Wassermann had been negative on several occasions. For a year he had felt weak and had many attacks of dizziness but had never actually lost consciousness. At times his heart "thumped" and he was a little short of breath. His heart was considerably enlarged, rate 28, sounds of good quality, no murmurs. Blood pressure, systolic 125, diastolic 50. Slight edema of the ankles. Before I saw him he had been given several courses of mercury, potassium iodid and arsphenamin without any appreciable effect. Later atropin, thyroxin and epinephrin were each tried but failed to influence the condition of block.

It is interesting to note that in both of these cases classified as lesions of the left bundle, there is associated a complete or partial block of the A-V bundle. This suggests the thought that the lesion producing the defect has invaded a portion of the main stem and the entire left bundle before it has reached the point where it subdivides.

The digitalization of these cases of bundle branch block affords several points of interest.

1. The patients usually develop extrasystoles at a comparatively early stage of digitalization.

2. The extrasystole is usually (not invariably) initiated in the ventricle opposite to the one in which the bundle is intact.

3. The Q-R-S complex is prolonged.

4. The T′ deflection is prolonged and increased in amplitude.

All of these features are illustrated in Chart 4. These records were secured from a man, aged 57, suffering from marked symptoms of cardiac insufficiency and attacks of precordial pain. He had a history of rheumatism when he was 27 and syphilis at 32. The blood Wassermann was positive. He presented a greatly enlarged heart with mitral and aortic valve lesions and a dilated aorta. Four months later he died very suddenly from a thrombosis of the right coronary artery. The curves indicate the changes in the three leads produced by digitalization.

Chart 5 is from a woman, aged 67, who is still living and has been under observation for four years. She has a general arteriosclerosis, an enlarged heart with lesions of the mitral and aortic valves and a dilated aortic arch. The etiology is obscure. There is no history of syphilis and the blood Wassermann reaction has been found negative repeatedly. She has had an auricular fibrillation and attacks of cardiac insufficiency during the whole period of observation. The records are presented for the purpose of comparing the curves obtained before and after the administration of digitalis. The electrocardiograms of each of these cases show a lesion of the right branch of the bundle. As has been pointed out by Lewis and by Wilson, the initial portions of the usual ventricular complex in these cases is written by the left ventricle (the "levocardiogram"). After digitalis was administered, extrasystoles appeared which arose in the right ventricle and the "dextrocardiogram" was written. It seems quite possible that these extrasystolic contractions may arise in the right branch of the bundle distal to the pathologic lesion.

The prolongation of both the Q-R-S group and the T′ complex indicates that digitalis has a very definite influence in inhibiting the rate of conduction in the ventricular tissues and is a corroboration of the observations on changes in the T-wave made by Cohn, Fraser and Jamieson in 1915.[2] These alterations also emphasize the generally recognized fact that digitalis has a much greater influence in hearts presenting pathologic changes than in those with normal tissues.

Lewis [3] in his studies of the spread of the excitatory process in the heart both experimentally in animals and in human records has charted the curves which are produced when the stimulus is received by one ventricle and then passes through the septum to activate the other ventricle. When the left ventricle primarily receives the stimulus the "levocardiogram" is written, when the right ventricle is the first to be stimulated the "dextrocardiogram" is recorded. The curve written by the ventricles of the normal subject (the "bicardiogram") is the algebraic sum of the "levocardiogram" and the "dextrocardiogram." Wilson [4] has studied the same subject by a clever and most original method; he cut the right branch of the bundle and recorded the "levocardiogram," he then stimulated the right ventricle and obtained the curve of the extrasystolic "dextrocardiogram." By introducing the

2. Cohn, Fraser and Jamieson: The Influence of Digitalis on the T-Wave of the Human Electrocardiogram, J. Exper. Med. **21**:593, 1915.

3. Lewis: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc. London **207**:221, 1916.

4. Wilson, F. N., and Herrmann, G. R.: Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229 (May) 1921.

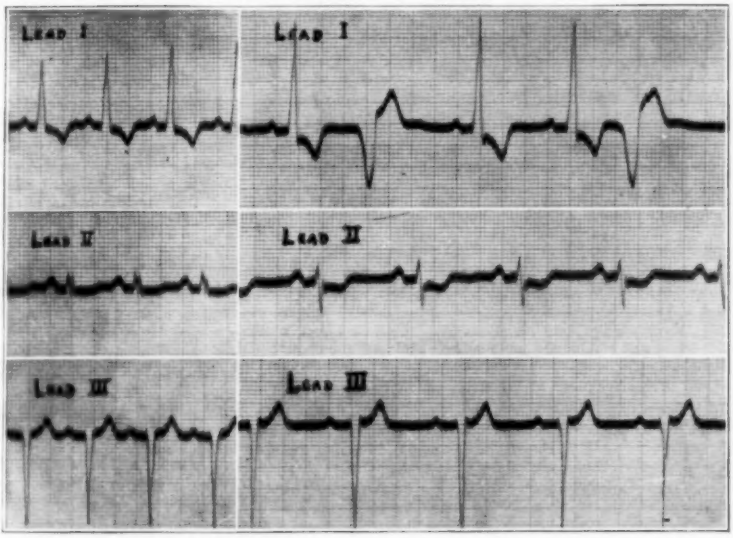

Fig. 4.—Before digitalis (left). After digitalis (right). Right bundle branch block. Levocardiogram. After digitalis two extrasystolic dextrocardiograms, Q-R-S prolonged, T′ prolonged and amplitude increased.

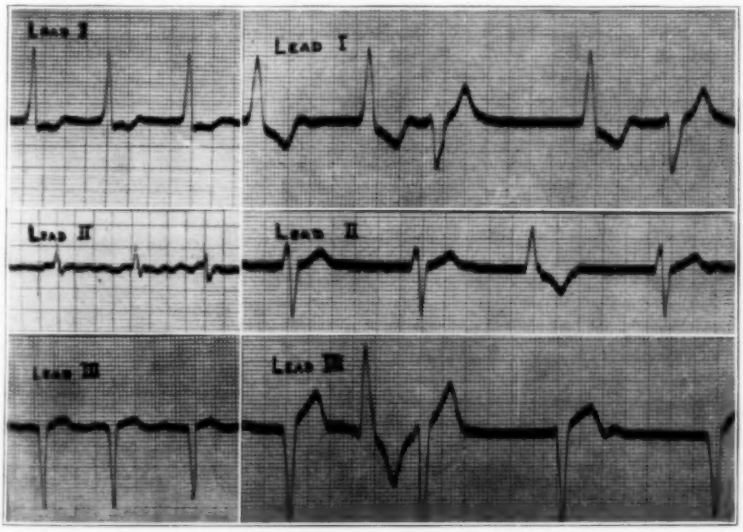

Fig. 5.—Before digitalis (left). After digitalis (right). Auricular fibrillation. Right bundle branch block. Levocardiogram. After digitalis many extrasystolic dextrocardiograms. Q-R-S prolonged, T′ prolonged, amplitude increased.

stimulus at the proper time so that the normal stimulus and the artificial stimulus were coincident, both ventricles were simultaneously activated and the curve written was the normal "bicardiogram."

In the clinic we occasionally encountered curves which have so many points of similarity to the curves which Wilson obtained experimentally that we are impelled to interpret them as produced by a corresponding mechanism.

In Charts 4 and 5 the stimuli coming down through the bundle activate the left ventricle and the "levocardiogram" is written; under the influence of digitalis the right ventricle becomes irritable and

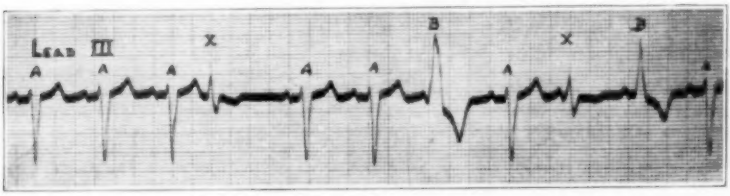

Fig. 6.—Lead III only. Right bundle branch block. Complexes A, levocardiograms. Complexes B, dextrocardiograms. Complexes X, bicardiograms.

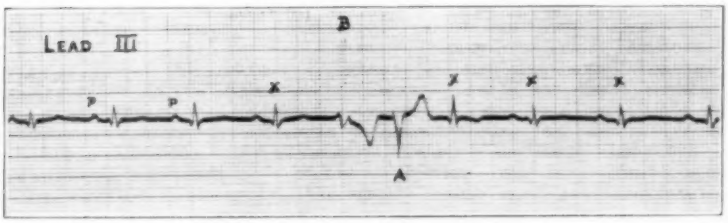

Fig. 7.—Lead III only. X, normal ventricular bicardiograms. A, extrasystolic levocardiograms. B, extrasystolic dextrocardiogram.

occasionally an extrasystolic "dextrocardiogram" appears. If, as Wilson has done experimentally, we could superimpose one of these curves on the other in the proper time relation the "bicardiogram" normal for this person would be recorded.

In Chart 6 is presented a curve which we believe may be explained by the mechanism that has been suggested. The record was obtained from a man, aged 55, a machinist, who was suffering from a general arteriosclerosis with cardiac hypertrophy, with a history of numerous attacks of cardiac insufficiency covering a period of five years. There was no definite history of infections of any kind, no rheumatism, the

blood Wassermann test was negative. He had edema of the legs and hydrothorax. He died suddenly a few days after the record here presented was taken.

Only Lead III is reproduced. We interpret this curve as indicating a lesion of the right branch of the bundle. The complexes marked "A" are characteristic levocardiograms written by the left ventricle in response to normal supraventricular stimuli. The complexes marked "B" are extrasystoles originating in the right ventricle (dextrocardiograms). We suggest that the complexes marked "X" are bicardiograms due to the simultaneous activation of the right and left ventricles.

A similar explanation is offered in the interpretation of Chart 7. This is the record from a man, aged 30, who supposed he was in perfect health with no subjective symptoms of any description. The irregularity of the heart was discovered in the course of a routine examination for life insurance and he was referred to me for further study and for an opinion as to his insurability. Only Lead III is reproduced. This curve is not one of bundle branch block, but is included in this series because it illustrates so well the extrasystolic levocardiogram, the extrasystolic dextrocardiogram and his normal bicardiogram. In this case the ventricular irritability was caused by the very excessive use of tobacco.

SUMMARY

Lesions of the right branch of the bundle of His are not uncommon.

Lesions of the left branch are rare, the electrocardiographic curves of two cases associated with complete A-V block are presented and discussed.

These lesions have been seen only in cases of advanced heart disease and a high mortality is to be expected.

The administration of digitalis produces conspicuous changes in the graphic records.

Several curves are presented illustrating the clinical analogues of the dextrocardiogram, levocardiogram and bicardiogram which others have produced experimentally.

160 West Fifty-Ninth Street.

OBSERVATIONS ON A CENTRIPETAL VENOUS PULSE IN MAN *

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If one seals a glass capsule over a superficial vein on the back of the hand and applies to this capsule an air pressure a few millimeters of water lower than the minimum pressure required to produce complete collapse of the vein, a distinct pulsation of the vein with each heart beat will be seen in a certain number of subjects. That this pulse is not transmitted directly back from the heart, as is the jugular pulse, is shown by the fact that the pulse persists after compression of the vein just central to the capsule. The pulsations are abolished by compression of the vein just peripheral to the capsule. It would appear that we are dealing with a pulse passing from the arteries through the capillaries and venules into the larger veins. With this idea in mind, certain procedures calculated to modify the extent to which a pulse could be propagated from the arterial to the venous side of the circulatory bed were carried out. These procedures were exercise and the application of heat and of cold.

The subject sits in the apparatus designed for stationary exercise described in a recent paper.[1] The pressure in the capsule is applied by the admission of compressed air.[2] Exercise consists in the lifting of 5 kg. weights by extension of the legs, the exercise period being five minutes. Heat was applied by partially immersing the hand in water at 45 C., cold by partial immersion in water at 5 C. Some subjects under no circumstances showed a venous pulsation. Others showed no pulse under control circumstances but it appeared on application of heat. A third group showed a pulse under control circumstances; this persisted and seemed to be somewhat accentuated on application of heat. In all cases the pulse was abolished on application of cold. A five minute exercise period seemed to have no influence in determining the presence or absence of the pulse. In one subject, who showed no pulse at rest, a fifteen minute period of exercise to the point of sweating brought out the pulse. In all cases where the venous pulsation is seen, the pulse at the radial artery is felt a fraction of a second before the venous pulse

* From the Physiological Department of Washington University.

1. White, H. L.: Circulatory Responses to Exercise in Man and Their Bearing on the Question of Diastolic Heart Tone, Am. J. Physiol. **69**:410 (July) 1924.

2. White, H. L.: Observations on Venous Pressure and Skin Blanching Pressure by a Modified Method, Am. J. Physiol. **69**:10 (June) 1924.

is seen. No attempt has been made to measure this interval quantitatively. A table illustrating some of the positive results is given, the presence or absence of the venous pulse being indicated.

Positive Results, Showing Presence or Absence of Venous Pulse

		Subject Z.	Age 55	
Control	Heat	Cold	Exercise	
absent	present	absent	absent	no compression
absent	present	absent	absent	central compression
absent	absent	absent	absent	peripheral compression
		Subject H.	Age 21	
Control	Heat	Cold	Exercise	
present	present	absent	absent	no compression
present	present	absent	absent	central compression
absent	absent	absent	absent	peripheral compression
		Subject D.	Age 28	
Control	Heat	Cold	Heavy Exercise	
absent	present	absent	present	no compression
absent	present	absent	present	central compression
absent	absent	absent	absent	peripheral compression

Our interpretation of these results is that in certain subjects heat and heavy exercise dilate the arterioles and capillaries to the extent that the pulse from the arteries is permitted to pass to the venous side. On heavy exercise, the increased pulse pressure also must play a part. With some subjects this condition obtains at rest, while with others it cannot be brought about even by the application of heat or by exercise. The constriction of the arterioles and capillaries by cold damps out the pulse. By the time the pulse reaches the venous side it possesses only a small amount of energy. It is thus not surprising that a manometer connected with a cannula in a vein should fail to register a pulse. The pulsations become evident only when the conditions are such that the maximum oscillations of the vessel wall are produced, i. e., when the externally applied pressure equals the diastolic venous pressure. Attempts to measure the pulse pressure in the vein on the basis of this principle have not proved practicable since the difference between systolic venous pressure (the minimum pressure required to produce complete collapse of the vein) and diastolic venous pressure (the pressure at which the maximum pulsations are seen) is at the most only a few millimeters of water.

Lewis [3] has recently reported localized "capillary pulsation" on the local application of heat. He finds on microscopic examination that

3. Lewis, T.: Observations upon Capillary Pulsation, J. Physiol. **58**:21, 1924.

the venules as well as the capillaries participate in this pulsation. He has traced the pulsation as far as "the larger venules of the subpapillary plexus" but makes no mention of having observed a pulse in large superficial veins. He finds that the pulse in the venules is centripetal, which agrees with our present findings on large veins. Krogh and Rehberg,[4] working with microscopic preparations of the bladder of the frog, find that the pulse wave penetrates capillaries but is annihilated by interference in the venules. It is apparent that this is not necessarily the case in man. Lewis also finds that "in middle life and more advanced years the reaction to heat, described in the foregoing, is usually reduced or absent; suggesting that the arterioles have lost, partially or completely, their power to expand." We have not found any definite relation between age and the venous pulse. A number of young subjects, aged from 20 to 25 years, have failed to show the pulse on exercise or application of heat, while of two middle-aged subjects available, one, aged 42, failed to show a pulse; the other, aged 55, showed no pulse under control circumstances, but it appeared on application of heat.

In view of the fact that it does not appear to be generally recognized, judging from the statements in current physiology texts, that a centripetal venous pulse propagated through the capillaries from the arteries may exist in normal subjects, it is interesting to note that King [5] in 1837 observed, with the aid of a mirror, pulsations of the large median veins of his own forehead while lying on his back about a half hour after dinner. He attributes this to the passage of the arterial pulse through the capillaries into the vein, but apparently did not exclude the possibility of a centrifugal pulse from the right heart. The same can be said of some of his observations on pulsations of veins on the back of the hand. The presence of valves need not necessarily block a retrograde pulse. More convincing, however, is King's reference to "an old experiment, to immerse the hand in warm water previous to and during venesection; when the jet of blood is distinctly seen to increase with each arterial pulse." He adds that this experiment will not always succeed. I believe that King is justified in his remark that this behavior of the escape of venous blood "is a sufficient proof that the impulse of the left ventricle is not always completely expended on the arterial or even on the capillary system."

Benson [6] refers to the escape of venous blood *per saltum* in one of his patients. This patient also showed distinct pulsation of the veins

4. Krogh, A., and Rehberg, P. B.: Kinematographic Methods in the Study of Capillary Circulation, Am. J. Physiol. **68**:153 (April) 1924.

5. King, W. T.: An Essay on the Safety-Valve Function in the Right Ventricle of the Human Heart, Guy's Hosp. Rep. **2**:104 (series 1) 1837.

6. Benson, C.: Case of Pulsation in the Veins of the Upper Extremities, Dublin J. M. Sc. **8**:324 (series 1) 1836.

of the upper extremities. Benson concludes that this pulsation depends on regurgitation from the right heart rather than a pulse from the left heart passing through the capillaries. Stokes [7] refers to this case, and agrees with Benson as to the mode of production of the pulse. It is difficult for me to see how such a view can be held. A necropsy showed that the venous valves were completely competent, and while I will readily admit that a retrograde pulse wave may well pass competent valves I cannot see how blood could be regurgitated. A more reasonable explanation is a centripetal pulse coming via the arteries and capillaries. Quincke [8] reports a centripetal pulse in the veins of the back of the hand in his own case and in two other cases without aortic insufficiency; one of these patients, however, presumably had paralysis of the vasomotor nerves to the region where the pulse was seen. He also reports four cases of aortic insufficiency, with presumably a high pulse pressure, in which the venous pulse was evident. He does not appear to recognize that the pulse may be of frequent occurrence in normal persons. "Under proper conditions, which may, in part, occur only pathologically, but which lie, in part, also within the limits of the normal, the pulse wave passes to the capillaries and even on into the veins." (Unter passenden Bedingungen, wie sie zum Theil nur pathologisch vorkommen, zum Theil aber auch durchaus in den Grenzen der Norm liegen, pflanzt sich die Welle bis in die Capillaren und selbst bis in die Venen fort.) In a later paper [9] Quincke further states that certain conditions are necessary for the production of the centripetal venous pulse; a considerable relaxation of the arterioles, a powerful heart beat, preferably with a high pulse pressure and, for its visualization, a thin skin and a certain medium degree of venous filling. The pulse is thus seen most frequently in fevers and is seen in normal subjects only when a high temperature has produced a marked vasodilatation. As was first suggested by Quincke, and later by Jürgensen,[10] the direct anastomoses between arterioles and venules reported by various anatomists may play a part in the production of the centripetal venous pulse.

It is apparent that Quincke's failure to recognize that this pulse is of rather frequent occurrence in normal subjects, even at ordinary temperatures, is due to the fact that he merely observed the veins without subjecting them to any external pressure. Under these condi-

7. Stokes, W.: Diseases of the Heart and Aorta, 1855, p. 219.

8. Quincke, H.: Beobachtungen über Capillar-und Venenpuls, Berl. klin. Wchnschr. **5**:357, 1868.

9. Quincke, H.: Ueber Capillarpuls und centripetalen Venenpuls, Berl. klin. Wchnschr. **27**:265, 1890.

10. Jürgensen, E.: Microkapillarbeobachtungen, Deutsches Arch. f. klin. Med. **132**:204 (May) 1920.

tions only relatively powerful pulsations could be recognized. Our success in demonstrating the pulse in a rather high percentage of normal subjects has been due to our subjecting the vein to a pressure at which the maximum oscillations of the vessel wall are brought out.

SUMMARY

Evidence is presented that a pulse may pass from the arterial to the venous side of the circulatory bed in normal subjects, and can be demonstrated in the large superficial veins.

THE VOLUME AND COMPOSITION OF THE BLOOD, AND THE CHANGES INCIDENT TO DIURESIS, IN CASES OF EDEMA

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The idea is prevalent among physicians that hydremia or hydremic plethora is the rule in cases of edema. This impression is based on (1) the pallor or so-called pasty appearance of the skin, (2) the decrease in urinary output, (3) the accumulation of water in the subcutaneous tissues or in the serous cavities, and (4) the decrease, in certain cases, in the percentage of solids, hemoglobin, albumin, erythrocytes, and so forth, in the blood and plasma. Although these findings are suggestive of an edematous or watery state of the blood, that is, of dilution of the blood by water which has failed of excretion, there has long been a wish that this general impression might be supported by more tangible and conclusive evidence.

Edema, although a familiar clinical phenomenon and the subject of innumerable investigations, is at present far from being understood. Since its experimental production is difficult, indeed practically impossible, our knowledge of the condition of the blood in cases of edema has been, and for the present must continue to be, derived from clinical sources. We know, however, that physicochemical processes, involved in the interchange of water between the blood and tissues, play a striking part. In the study of this interchange of fluid, the great importance of data pertaining to the volume and composition of the blood is obvious. In fact, such data are essential in determining whether changes occurring in liquid and solid constituents of the blood are actual or relative. Lack of suitable methods of determining blood and plasma volumes during life have been responsible for the dearth of data relative to absolute values. With the advent of the dye method of determining circulating blood and plasma volumes, this difficulty has been diminished to a great extent, and it seems highly desirable at this time to investigate again the subject of the concentration and volume of the blood in relation to edema.

Various Conceptions of Hydremia.—In reviewing the literature on the composition of the blood in cases of edema, the terms "hydremia," "hydremic plethora" and "hydremic state" constantly occur. Bright observed the watery condition of the blood in the edema of nephritis, and attributed this to loss of albuminous substances into the urine with

thinning of the blood. Stewart introduced the term hydremic plethora to indicate a dilution of the blood by the addition of water. Cohnheim,[1] in his classical studies on hydremia and anhydremia in relation to edema, says: "The blood is hydremic when the contained water is absolutely or relatively increased." In case of absolute increase, the total amount of solid constituents in the blood (chiefly albumin) remains unaltered, but the amount of water is increased. In case of a relative increase, the albumin is diminished, while the weight and volume of the water are normal. Cohnheim also recognized a third theoretic possibility, that of diminished albumin content associated with an increased total content When this combination of changes occurs, it must indeed cause an especially severe degree of hydremia. Dieballa[2] narrowed the conception of hydremia to a condition in which the plasma solids are relatively or absolutely decreased. A relative decrease is caused by an increase of the total blood with dilution of the solids, that is, by hydremic plethora, while an absolute decrease is due to an actual loss of plasma proteins.

Boycott[3] found that in the edema of experimental uranium nephritis in animals, the blood, as well as the tissues, was affected, and that the condition was associated with serous effusions. Hemoglobin values were employed as criteria of the so-called hydremia. Volhard[4] asserts that blood dilution or hydremia, with a relative decrease of erythrocytes of from 1,000,000 to 2,000,000, is often associated with glomerular nephritis, but that this condition does not predominate in cases in which the edema is marked. He cites Ebert, who, using Bang's micromethod for estimating blood water, finds that blood water and edema are inversely related in certain cases. The blood water may be lowest in the periods of greatest edema, it may increase with absorption, and may even further increase with the restoration of the glomerular function. A lowering of the erythrocytes for each unit volume and an increase in blood volume have been observed in this later period. Volhard calls attention to the loose usage of the term hydremia. He would limit it to indicate a condition of the blood in which there is an actual dilution, with a resulting percentage reduction of the cellular elements. He questions its usage in relation to conditions in which the blood merely exhibits diminished solids.

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1. Cohnheim, J.: Lectures on General Pathology, a Handbook for Practitioners and Students, London, New Sydenham Society, 1889, p. 447.

2. Dieballa, G., and Kétly, V.: Ueber die Wechselbeziehung von Albuminurie, Hydrämie, und Hydrops bei Brightikern, Deutsch. Arch. f. klin. Med. **61**:76-90, 1898.

3. Boycott, A. E.: The Regulation of the Blood Volume in Normal and Nephritic Animals, J. Path. & Bacteriol. **18**:498-512, 1913-1914.

4. Volhard and Fahr: Die doppelseitigen hematogenen Nierenerkrankungen, Berlin, Julius Springer, 1918.

Keith, Rowntree and Geraghty,[5] in their original report on the use of the vital red method of determining blood volume, noted no significant changes in plasma volume during the period of diuresis in a case of renal edema. Bock,[6] using the dye method for estimating plasma volume in case of edema, found no disturbance of the relationship between plasma volume and body weight. Lindner, Lundsgaard and Van Slyke[7] studied the plasma proteins in cases of nephritic edema, and found that actual depletion, and not dilution, was the basis for the low protein values. The amount of the total plasma protein for each kilogram of body weight was definitely diminished (from 1.5 to 3.0 gm.), the normal values being from 3.0 to 5.0 gm. The body weight was corrected for the probable additional weight of edema fluid.

There is considerable difference of opinion with regard to the state of the blood in cases of cardiac edema. Many investigators maintain that a normal water content of serum is present; Strauss[8] and Veil[9] believe that increased water content of serum exists in certain cases. Chiray[10] has observed increased concentration of the blood in certain stages of cardiac edema. Bolton,[11] in an experimental study of cardiac edema produced by partial obstruction of the inferior vena cava, using the Welcker method for determining blood volume, found hydremic plethora, which subsequently became converted into a true plethora by the entrance of erythrocytes into the blood. There are no available data on the volume and composition of the blood in cases of diabetic edema.

To correlate the diverse conceptions, held at the present time, of the composition of the blood in cases of edema is almost impossible, because of (1) lack of data relative to absolute values in relation to the solids and water of the blood and plasma, (2) lack of comparative data in the different types of edema, and (3) confusion and inadequacy of terms used in relation to blood states. In the work herein reported,

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5. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547-576 (Oct.) 1915.

6. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83-101 (Jan.) 1921.

7. Lindner, J. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E.: The Cause of Low Plasma Protein Concentration in Nephritis, Proc. Soc. Exper. Biol. & Med. **20**:319, 1923.

8. Strauss, H.: Untersuchungen über den Wassergehalt des Blutserums bei Herz- und Nierenkranken, Ztschr. f. klin. Med. **60**:501-505, 1906.

9. Veil, W. H.: Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, Deutsch. Arch. f. klin. Med. **112**:504-538, 1913; ibid., Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, Deutsch. Arch. f. klin. Med. **113**:226-260, 1914.

10. Chiray, M.: Dilution et concentration du sang, Presse méd. **16**:19-22, 1908.

11. Bolton, C.: Further Observations on the Pathology of Cardiac Dropsy, J. Path. & Bacteriol. **20**:290-326 (Jan.) 1916.

we have attempted to obviate some of these difficulties by collecting data in different types of edema, by the correlation of absolute and relative volumes, and by use of new terms to indicate the volume states.

New Terminology for Volume States of the Blood.—In view of the conflicting interpretations of hydremia, hydremic states, hydremic plethora and polyemia, and of the resultant confusion, it seems wiser to avoid the use of these terms in discussing blood volume. If the term hydremia is to be retained, we believe it should be limited to indicate increased water content of plasma. With these points in mind, terms as follows are suggested: (1) normovolemia for normal blood volume, (2) hypervolemia for increased blood volume, and (3) hypovolemia for

TABLE 1.—*Classification and Suggested Terminology of Volume States of the Blood*

Normovolemia for Normal Blood Volume:
A. Simple normovolemia for normal ratio of cell to plasma volume
B. Polycythemic normovolemia for increased ratio of cell to plasma volume Synonym—Concentrated blood
C. Oligocythemic normovolemia for decreased ratio of cell to plasma volume Synonym—Anemia
Hypervolemia for Increased Blood Volume:
A. Simple hypervolemia for normal ratio of cell to plasma volume Synonym—Simple plethora, observed in certain types of edema
B. Polycythemic hypervolemia for increased ratio of cell to plasma volume Synonym—Polycythemia vera
C. Oligocythemic hypervolemia for decreased ratio of cell to plasma volume Synonym—Hydremic plethora, seen in some anemias
Hypovolemia for Decreased Blood Volume:
A. Simple hypovolemia for normal ratio of cell to plasma volume Synonym—Simple oligemia, observed immediately following blood loss and in certain cases of edema and obesity
B. Polycythemic hypovolemia for increased ratio of cell to plasma volume Synonym—Anhydremic oligemia. Anhydremia, observed in shock and dehydration states
C. Oligocythemic hypovolemia for decreased ratio of cell to plasma volume Synonym—Oligocythemia, occasionally observed in anemia

decreased blood volumes. These terms are self-explanatory and apply only to volume states. Obviously, the cell plasma volume ratio also is important, entering into consideration in all physiologic or pathologic changes in volume and composition of the blood. In expressing this ratio, modifying terms may be employed, such as (1) simple for normal cell plasma volume ratio, (2) polycythemic for increased cell plasma volume ratio, and (3) oligocythemic for decreased cell plasma volume ratio (Table 1).

Types of Cases Studied.[12]—The present study embraces (1) three cases of cardiac edema,[13] (2) three of diabetic edema, (3) four of subacute glomerular nephritis with edema, and (4) four of subacute nephrosis.

12. These cases were uncomplicated by an acute or subacute infection such as rheumatism, endocarditis or nephritis.

13. The clinical diagnoses were made independently by clinicians to whom the cases were assigned.

Method of Collecting Blood.—Blood was taken from the patient between the hours of 8 and 9 a. m., with the patient at rest and fasting, and no fluids having been taken. The blood and plasma volumes in relation to body weight were calculated for the postedema period. As the period between the edema and postedema estimations was relatively short, in all but one case, the error incident to weight changes, other than those caused by water loss, was small, and would not, of course, invalidate the total volume values.

Treatment.—The standard Karell diet with digitalization was routinely employed in the cases of cardiac edema. The fluid intake was restricted for the entire period between the estimations. Massive calcium treatment with moderately restricted fluids was given in cases of the diabetic type of edema, besides the specific treatment for diabetes.

The usual salt free, low protein regimen was the rule in cases of glomerular nephritis. In Cases 7 and 10, abdominal paracentesis was performed; in Cases 8, 9 and 10, sweating and calcium treatment were employed without results; in cases of nephrosis, the treatment consisted of salt free diet and fluids restricted to from 600 to 800 c.c. Massive doses of calcium were tried in Case 11 without noticeable results.

METHODS EMPLOYED IN ESTIMATING BLOOD CONTENT, BLOOD VOLUME AND SO FORTH

1. Circulating blood and plasma volumes were determined by the original dye method of Keith, Rowntree and Geraghty, vital red and Congo red being used interchangeably. In order to prevent coagulation, 1 c.c. of a 1.6 per cent. solution of sodium oxalate was evaporated from centrifuge tubes, the oxalate being deposited uniformly in fine, powdered form on the inner surface of the tubes.[14] In hematocrit determinations, three 10 c.c. standardized, graduated centrifuge tubes were used, the average or mean reading constituting the basis for calculating hematocrit values. In the colorimetric readings, the Duboscq colorimeter was used exclusively.

2. The water and solid contents of the blood were determined gravimetrically, before and after drying in vacuo over phosphorus pentoxid at room temperature. Drying was continued until the weight became constant. Duplicate estimations were made in every instance, and average values taken. In the earlier stages of the work, specific gravity determinations were made by the pyknometric method, but these were subsequently discontinued, as they were not deemed essential.

3. The cell water calculations were made by means of the formula: $x = \frac{A - (B \times C)}{D}$ in which A represents the percentage of water

14. With this technic, hemolysis rarely occurs.

in whole blood; B, the percentage of water in the plasma; C, the percentage of plasma by hematocrit, and D, the percentage of cells by hematocrit.

4. For hemoglobin determinations, the Palmer method was used. In several instances, the values thus obtained were checked with an acid hematin method devised by Osgood.

TABLE 2.—*Table of Normal Values in Fifty Cases*

	Range	Average
Blood water, per cent.	79 to 83	81
Plasma water, per cent.	91 to 93	92
Cell water, per cent.	60 to 68	64
Total circulating blood volume (according to the dye method), c.c.	4,930 to 7,430	6,180
Blood volume for each kilogram of body weight, c.c.	72 to 100*	86
Blood volume for each square meter surface area, c.c.†	2,550 to 4,010	3,360
Total circulating plasma volume (according to the dye method), c.c.	2,960 to 4,160	3,610
Plasma volume for each kilogram of body weight, c.c.	43 to 59	52
Plasma volume for each square meter of surface area, c.c.	1,420 to 2,250	2,050
Total circulating cell volume, c.c.	1,970 to 3,310	2,550
Hematocrit cells, per cent.	38 to 45	41

		Hemoglobin	
Author	Determinations	Men, Gm. for Each 100 C.c.	Women, Gm. for Each 100 C.c.
Liehenstern	61	14.14	13.10
Williamson	900	16.00	15.55
Haldane and Smith	12	13.80	13.80
Haden (calculated on a red cell count of 5,000,000)	...	15.65	15.56

* Total volume values as high as 105 c.c. for each kilogram of body weight have been found in three normal controls. This group needs further study.

† Dreyer contends that blood volume is a function of surface area rather than body weight.

TABLE 3.—*The Percentage Variation of Error Believed to be Inherent in the Different Methods*

	Per Cent.		Per Cent.
Blood volume	5.0	Cell water	2.0
Plasma volume	2.5	Hemoglobin	2.0
Blood water	0.5	Hematocrit	2.0
Plasma water	0.5		

5. The total circulating hemoglobin was determined from Haldane's [15] normal value of 13.8 gm. of hemoglobin for blood, with oxygen capacity of 18.5 per cent. by volume. According to the following calculations, total percentage hemoglobin times 13.8 times total blood volume equals total circulating hemoglobin. The probable variations of error in methods employed may be noted in Table 3.

15. In this country, higher values have been obtained by Williamson and Haden (Table 2).

TABLE 4.—*Repeated Determinations of the Volume and Concentration of the Blood in Normal Persons*

Case	Date	Weight, Kg.	Hemoglobin		Hematocrit Cells, per Cent.	Blood Volume, C.c.			Plasma Volume, C.c.			Cell Volume, C.c.	Water, per Cent.		
			Per Cent.	Total Circulating, Gm.		Total	Each Kg.	Each Sq. M.	Total	Each Kg.	Each Sq. M.		Blood	Plasma	Cell
1	11/ 7/23	58	150	1,146	45	5,540	95	3,400	3,050	52	1,850	2,490	77.4	91.7	60.5
	11/ 9/23	58	132	976	43	5,340	92	3,250	3,050	52	1,850	2,290	80.2	92.6	63.7
2	11/ 7/23	51	114	777	40	4,930	96	3,170	2,960	58	1,910	1,970	80.1	91.6	62.8
	11/11/23	51	112	769	40	4,980	97	3,210	2,990	58	1,930	1,990	81.9	92.6	65.8
3	11/13/23	68	115	1,056	40	6,660	98	3,660	4,000	59	2,190	2,660	82.3	94.4	64.0
	11/15/23	68	113	1,005	43	6,440	94	3,540	3,670	54	2,020	2,770	80.3	92.6	64.0
4	11/30/23	60	114	837	38	5,320	88	3,160	3,300	54	1,940	2,020	80.3	91.9	66.4
	12/ 3/23	60	111	882	41	5,760	96	3,430	3,400	56	2,010	2,360	81.9	92.5	66.7
5*	12/ 1/23	72	115	935	43	5,900	82	3,120	3,360	46	1,780	2,540	79.8	92.2	63.2
	12/ 8/23	71	116	1,054	40	6,560	93	3,520	3,950	55	2,110	2,640	81.5	93.4	63.7
	12/15/23	70	103	936	40	6,560	94	3,580	3,950	56	2,120	2,640	83.0	93.2	67.5
6	12/ 3/23	68	109	1,028	41	6,850	100	3,810	4,040	59	2,230	2,810	80.5	91.6	63.7
	12/ 5/23	68	108	1,004	40	6,740	99	3,740	4,040	59	2,230	2,690	80.5	92.0	63.2
7	12/ 4/23	70	115	1,167	45	7,360	105	3,960	4,050	56	2,190	3,310	79.6	93.3	63.2
	12/ 7/23	70	116	1,188	44	7,430	106	4,010	4,160	59	2,250	3,270	80.4	93.2	64.0
8	12/ 6/23	80	113	1,114	44	7,140	89	2,550	4,000	50	1,425	3,140	80.0	92.3	64.0
	12/10/23	80	119	1,192	45	7,270	90	2,560	4,000	50	1,425	3,270	80.8	93.2	65.7
9	12/ 8/23	66	107	873	36	5,920	87	3,200	2,790	55	2,050	2,130	82.0	93.5	61.8
	12/10/23	66	107	929	38	6,310	92	3,430	3,910	57	2,110	2,400	82.3	93.5	64.0
10	12/13/23	71	122	991	42	5,350	75	3,020	3,100	43	1,750	2,240	81.3	94.2	63.5
	12/17/23	71	113	799	39	5,140	72	2,990	3,130	44	1,770	2,000	82.6	92.9	66.5
Average values....			114		41	6,180	88	3,360	3,610	53	2,050	2,555	80.9	92.7	64.2

* Dec. 4, 1923, tonsillectomy.

NORMAL VALUES WITH METHODS EMPLOYED (TABLES 2 AND 4)

1. The circulating plasma volume in normal persons, as determined by the dye method, varies from 43 to 59 c.c., the average being 53 c.c. for each kilogram of body weight. There is fairly marked constancy in plasma volume in health. In obese persons, as has been shown,[16] the plasma volume is relatively lower.

2. In normal persons the relation of circulating blood volume to body weight varies from 72 to 100 c.c., with an average of 86 c.c. for each kilogram of body weight.

3. The blood water, according to Müller, averages 79.11 per cent. in men, with a variation of ± 1 per cent. In women, the average value is 81.01 per cent. with a variation of ± 1 per cent. In our normal cases the results agreed closely with these values. We believe that slight variations cannot be regarded as abnormal, a 1 to 2 per cent. fluctuation in the blood water concentration being observed during the course of a day in normal persons. We are arbitrarily increasing the limits of normal variation, the normal range being considered to be between 79 and 83 per cent. for men and women.[17]

16. Brown, G. E., and Keith, N. M.: Blood and Plasma Volume in Obesity, Arch. Int. Med. **33**:217-223 (Feb. 15) 1924.

17. The maximal variation in thirty hematocrit estimations, using the three large tube method, was 2 per cent. The average variation was 0.7 per cent.

4. The plasma water in men and women, according to our data, varies from 91 to 93 per cent., the average being 92.5 per cent. Calculations on the same person at different periods show a fluctuation as high as from 1 to 2 per cent.

5. The cell water, as determined by centrifugating and drying is, according to Biermacht, between 70 and 72 per cent. Bic and Müller estimate 65.4 per cent. for men and 64.81 per cent. for women, and Schmidt estimates 68.8 per cent. for a man, aged 25.[18] The drying method may be open to criticism, but we find that the calculation-hematocrit method yields values closely approximating those quoted. We find that the normal cell water varies from 60 to 68 per cent. The average in fourteen calculations was 64 per cent. A variation of 6 per cent. in the normal person during the day was observed.

6. The hematocrit values ranged from 38 to 45 per cent. for the cells, and from 55 to 62 per cent. for the plasma. The average for both men and women was 60 per cent. plasma and 40 per cent. cells. A daily variation of 2 per cent. is observed in normal persons.

7. The normal standard of hemoglobin is as yet unsettled; this is somewhat surprising in a substance so important. Table 2 presents some of the different hemoglobin values accepted as normal by various investigators.

VOLUME STATES IN EDEMA

In order to contrast the magnitude of the changes in blood volume and composition in normal persons with that in patients with edema and those who have had diuresis, repeated determinations of blood and plasma volume, and of the water content of blood, plasma and red cells, have been made on a group of fourteen persons. The period between the determinations has varied from two to fourteen days.

One is wont to regard the blood changes associated with edema and diuresis as due merely to the addition or withdrawal of water. It seems to us that this position is untenable, and that it is necessary to take into consideration changes in volume of the blood, plasma and cells, hemoglobin and protein. In this study we are attempting to analyze the various changes and to present what appear to us plausible explanations of the phenomena encountered. We realize that we are inviting criticism, but believe that the importance of the subject justifies our attempt.

Before entering into the actual analysis of the results of our studies, it is necessary to enumerate the processes which are probably involved in changes in the volume of plasma and cells and their composition.

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18. We recognize the sex differences in the blood water concentration, due to lower content of hemoglobin in females, but believe these variations are so slight as to be negligible in this study.

Obviously, there may be (1) addition or withdrawal of water, of plasma, and of cells, (2) addition or withdrawal of solids of plasma and cells, and (3) the addition or withdrawal of plasma, or cells as such. The process consists, then, in the dilution or concentration of cells and plasma, which affects composition and volume, or the addition or withdrawal of blood, which affects volume chiefly. The processes encountered are complex, and probably involve changes in water, solids, volume of blood, and plasma and cells in varying degrees in different forms of edema.

It has been quite generally believed that a large blood volume with a decreased cell plasma volume ratio, oligocythemic hypervolemia, or a dilution state, exists in certain cases of edema. This conclusion was reached by observations on the erythrocyte and hemoglobin content of the blood, or the plasma protein content. Deductions concerning blood volume obtained by such a method are open to serious objection, as fluctuations in percentage values for blood cells and other blood solids do not necessarily reflect volume fluctuation. Neither does the plasma protein content bear any fixed relation to plasma volume, and changes in plasma protein may denote either actual quantitative or relative fluctuation in protein or water content. It would seem, therefore, that more accurate quantitative data should be assembled in individual instances, and that conclusions relative to volume changes should not be based solely on changes in concentration of blood or plasma.

This study, therefore, presents certain volume data obtained by the dye method and, we believe, throws new light on the blood state in edema. In the four types of edema studied, increased circulating volume, or hypervolemia, is found in four cases (Cases 1, 2, 6 and 14, Tables 5 and 6). These were instances of simple hypervolemia, as the normal cell plasma volume ratio was not disturbed except in one instance (Case 14), in which chronic anemia was present, oligocythemic hypervolemia. It is difficult to determine whether the increased blood volume represented a state of dilution or actual anemia. The accumulation of water in the blood sufficient to produce a maintained oligocythemic hypervolemia or a relative anemia is, on theoretic grounds, improbable. Dilution, if it occurs, is probably transitory and of short duration, as was shown in experimental cardiac edema by Bolton, and after forced water ingestion, by Greene and Rowntree. The blood, like the other tissues and organs of the body, is provided with a mechanism safeguarding against excessive fluid accumulations. When elimination by the kidney is blocked, the tissues take up the excess water from the blood. In this respect, edema can be considered a protective phenomenon. The serous cavities and the intestines, under stress, also provide safety outlets. When the blood volume is increased by the addition of water, physiologic mechanisms, if available, tend to reestab-

TABLE 5.—*Total Circulating Volume and Water of the Blood in Edema and Postedema Periods**

Case	Diagnosis	Date	Weight, Kg.	Edema	Hemoglobin		Circulating Volume, C.c.			Total Water, C.c.		
					Per Cent.	Total Circulating, Gm.	Blood	Plasma	Cell	Blood	Plasma	Cell
1	Mitral endocarditis with myocardial insufficiency	6/ 1/22	75.5	4	90	830	6,700	4,090	2,610	5,780	3,900	1,900
		6/19/22	64.5	0	104	1,095	7,650	4,445	3,210	6,240	4,000	2,170
2	Mitral endocarditis with myocardial insufficiency	7/19/22	68.0	3	105	915	6,280	3,830	2,450	5,290	3,620	1,690
		8/16/22	54.0	0	86	700	6,430	3,733	2,709	5,430	3,500	1,850
3	Hypertension, myocardial insufficiency, obesity	2/12/22	108.0	3	100	830	5,940	3,565	2,376	5,000	3,340	1,660
		2/23/22	92.0	1	92	680	5,380	3,379	2,010	4,580	3,300	1,280
4	Diabetes mellitus	8/17/23	74.5	2	105	885	5,820	3,955	1,860	4,860	3,600	1,210
		8/22/23	69.5	0	108	880	5,950	3,900	1,970	4,960	3,730	1,220
5	Diabetes mellitus	4.10/23	83.0	3	132	1,090	6,000	3,600	2,400	4,680	3,350	1,320
		5/ 1/23	70.0	0	90	795	6,420	4,490	1,930	5,450	4,090	1,310
6	Diabetes mellitus	9/24/23	91.0	2	120	1,125	6,800	4,285	2,510	5,470	3,940	1,510
		10/ 8/23	63.0	0	104	825	5,740	3,673	2,066	4,660	3,400	1,150
7	Subacute glomerular nephritis	9/30/22	58.0	3	69	230	3,620	2,500	1,120	3,110	2,340	720
		10/20/22	51.0	1	63	300	3,520	2,650	870	3,050	2,470	600
8	Subacute glomerular nephritis	8/ 7/23	91.0	4	82	490	4,380	3,355	1,050	3,790	3,150	720
		9/11/23	66.0	0	89	500	4,100	2,926	1,170	3,570	2,750	830
9	Subacute glomerular nephritis	6/ 1/23	65.0	3	40	220	4,050	3,605	440	3,600	3,320	280
		7/ 3/23	56.5	1	52	235	3,300	2,640	660	2,800	2,420	380
10	Subacute glomerular nephritis	11/15/22	61.0	3	80	330	3,050	2,285	760	2,570	2,100	540
		1/ 5/23	48.0	0	51	220	3,200	2,600	600	2,830	2,450	380
		9/26/23	52.0	0	100	480	4,610	2,910	1,700	4,000	2,720	1,280
11	Subacute nephrosis	10/ 1/23	84.0	2	128	1,170	6,680	3,674	3,006	5,340	3,440	1,890
		10/23/23	74 0	0	124	1,130	6,620	3,710	2,910	5,370	3,490	1,880
12	Subacute nephrosis	10/ 7/22	94.0	4	119	1,120	6,830	4,235	2,595	5,630	3,950	1,670
		11/29/22	86.0	2	84	780	6,720	4,235	2,480	5,670	3,990	1 690
13	Subacute nephrosis	2/20/23	83.0	3	113	1,060	7,010	4,135	2,870	5,700	3 910	1,830
		5/16/23	75.0	0	115	1,060	6,860	4,119	2,740	5,400	3,800	1,620
14	Nephrosis, chronic osteomyelitis	8/18/23	65.0	3	91	740	6,010	4,571	1,440	5,630	4,140	890
		8/31/23	56.0	0	95	702	5,400	4,150	1,250	4,640	3,900	750

* According to the dye method for estimating blood volume.

TABLE 6.—*Relative Volumes and Concentration of the Blood in Edema and Postedema Periods**

Case	Diagnosis	Date	Edema	Hemoglobin, per Cent.	Hematocrit Cells, per Cent.	Water			Circulating† Volume, C.c. for Each Kg.		Relative Volume State, New Nomenclature
						Blood, per Cent	Plasma, per Cent.	Cell, per Cent.	Blood	Plasma	
1	Mitral endocarditis with myocardial insufficiency	6/ 1/22	4	90	39	86.3	95.3	73.0	104	64	Hypervolemia simplex
		6/19/22	0	104	42	81.6	91.4	66.0	119	69	Hypervolemia simplex
2	Mitral endocarditis with myocardial insufficiency	7/19/22	3	106	39	84.3	94.5	68.0	114	68	Hypervolemia simplex
		8/16/22	0	86	42	84.5	93.7	71.4	116	68	Hypervolemia simplex
3	Hypertension, myocardial insufficiency, obesity	2/12/22	3	100	40	84.3	93.6	70.0	64	39	Hypovolemia simplex
		2/23/22	0	92	37	85.5	94.1	70.0	58	37	Hypovolemia simplex
4	Diabetes mellitus	8/17/23	2	105	32	85.6	91.6	66.0	83	56	Oligocythemic normovolemia
		8/22/23	0	108	33	83.5	93.9	62.0	85	56	Oligocythemic normovolemia
5	Diabetes mellitus	4/10/23	3	132	40	78.0	93.3	55.0	81	51	Normovolemia simplex
		5/ 1/23	0	90	30	86.0	92.3	68.0	91	64	Oligocythemic normovolemia
6	Diabetes mellitus	9/24/23	2	120	37	80.5	92.1	60.0	108	68	Hypervolemia simplex
		10/ 8/23	0	104	36	81.3	92.6	56.0	91	58	Normovolemia simplex
7	Subacute glomerular nephritis	9/30/22	3	60	31	86.3	93.7	66.0	71	50	Oligocythemic hypovolemia
		10/20/22	1	63	25	86.6	93.6	66.5	70	52	Oligocythemic hypovolemia
8	Subacute glomerular nephritis	8/ 7/23	4	82	25	86.5	94.4	69.0	66	49	Oligocythemic hypovolemia
		9/11/23	0	89	29	87.2	94.2	69.5	62	44	Oligocythemic hypovolemia
9	Subacute glomerular nephritis	6/ 1/23	3	40	11	88.6	92.2	59.0	73	63	Oligocythemic normovolemia
		7/ 3/23	0	52	20	84.7	91.9	55.0	58	46	Oligocythemic hypovolemia
10	Subacute glomerular nephritis	11/15/22	3	80	25	84.3	91.9	70.0	63	47	Oligocythemic hypovolemia
	Tonsillectomy	1/ 5/23	0	51	19	88.7	94.5	64.0	66	54	Oligocythemic hypovolemia
		9/26/23	0	109	37	86.8	93.5	75.0	89	55	Normovolemia simplex
11	Subacute nephrosis	10/ 1/23	2	128	45	80.0	93.8	63.0	90	49	Normovolemia simplex
		10/23/23	0	124	44	81.1	94.2	64.0	89	50	Normovolemia simplex
12	Subacute nephrosis	10/ 7/22	4	119	38	83.1	94.4	64.1	79	49	Normovolemia simplex
		11/29/22	2	84	37	84.7	94.4	68.0	78	49	Normovolemia simplex
13	Subacute nephrosis	2/20/23	3	113	41	82.2	94.7	64.0	93	55	Normovolemia simplex
		5/16/23	0	115	40	78.7	91.7	59.0	91	55	Normovolemia simplex
14	Nephrosis, chronic osteomyelitis	8/18/23	3	91	24	85.9	92.5	63.0	107	81	Oligocythemic hypervolemia
		8/31/23	0	95	25	85.9	94.8	60.0	96	72	Oligocythemic normovolemia

* According to the dye method for estimating blood volume.
† Calculated on the basis of body weight of the postedema period.

lish the normal cell plasma volume ratio, either by getting rid of water or by adding erythrocytes and hemoglobin, as shown experimentally by Bolton. The latter may have taken place in Cases 1 and 2 of the cardiac group. If these measures fail, a maintained or chronic oligocythemic hypervolemia or anemia would exist theoretically, as in edema superimposed on preexisting anemia. Case 14 may be an example of this type. In the majority of cases of chronic anemia, either normal or decreased total blood volume values exist according to the dye method, with a decreased cell plasma volume ratio (oligocythemic normovolemia, or oligocythemic hypovolemia); oligocythemic hypervolemia has been found more rarely. In Case 1, during the period of edema, there was simple hypervolemia, which became more marked following diuresis, the cell plasma volume ratio remaining normal. In Case 2, likewise, a simple hypervolemia was present during the edema period which was maintained during diuresis, although some actual loss of hemoglobin occurred. It would appear that diuresis, per se, played only a minor part in these two cases in modifying the abnormal volume state, once it was established (Table 6). One has to admit the possibility that hypervolemia may precede the development of edema in some forms of cardiac disease.

In order to determine whether there is dilution of the blood, repeated volume and hemoglobin determinations are necessary. Lacking the volume and composition data for the period preceding, it is impossible to determine from a single examination whether a dilution state exists in the edema period. Degrees of dilution sufficient to produce a relative anemia would be suspected in the presence of an oligocythemic hypervolemia. The subsequent determinations would reveal the constancy or inconstancy of the volume and hemoglobin values. If these are inconstant, the degrees of dilution or concentration accompanying diuresis may be revealed by a comparison of percentage change in the actual and in the percentage hemoglobin. (When the percentage hemoglobin shows a greater percentage fluctuation than the actual circulating hemoglobin, a dilution or concentration process may be suggested.) When the percentage hemoglobin shows a greater percentage reduction than the actual hemoglobin, an increase in total blood volume will probably be found, or, when the percentage hemoglobin shows a greater percentage increase than the actual hemoglobin, it may be explained by volume decrease. In the study of the water exchange in edema, many variations in the volume-water-solid factors are found. Simple adjustments are rarely encountered; complex adjustments involving all three of the variables are the rule.

In Cases 7, 8 and 10, of glomerular nephritis, decreased total blood volume with decreased cell plasma volume ratio, or oligocythemic hypo-

volemia, existed in both the edema and nonedema periods. In Case 9, there was a borderline normovolemia in the edema period; this is an interesting observation, since it agrees with our previous studies on the anemia of chronic glomerular nephritis, which demonstrate that anemia is an integral part of this disease. We believed that the conditions would probably be the same in the more acute forms of this type of nephritis; the results of the present study confirm this, and apparently prove that a state of dilution is not instrumental in causing the anemia of glomerular nephritis. Such a deduction might be expected on *a priori* grounds because of the marked avidity with which the tissues take up water in this disease. The experimental work of McClure and Aldrich[19] is further proof of this "tissue thirst." The existence of anemia explains the high percentage of blood water found in certain types of nephritis, and has probably given rise to the conception of "hydremic condition of the blood." The volume changes in this group during diuresis were practically negligible, except in Case 9, in which there was a decrease in plasma volume and an increase of actual hemoglobin, apparently indicating a partial recovery from the anemia.

In Case 3 (cardiac edema in an obese woman), the relative blood and plasma volumes were low, which can be explained on the basis of obesity. In this case there was an actual reduction in cell volume and circulating hemoglobin during diuresis. The ratio of actual and percentage hemoglobin change was the same, showing that dilution played no part in the decrease of percentage hemoglobin. Normal volume states, or normovolemia, predominated in the cases of diabetes and nephrosis, both in the edema and nonedema periods. In uncomplicated cases of nephrosis, there apparently was no anemia, which finding may be of importance in the differential diagnosis of nephrosis and glomerular nephritis. It has been observed, however, that in many of the cases of so-called nephrosis, there eventually is increased blood pressure and other evidence of involvement of glomerular function.

VOLUME CHANGES FOLLOWING DIURESIS

In Cases 1, 6 and 9, volume changes were noted following loss of fluid (Table 7). In Case 1 (cardiac edema), there was an increase of 950 c.c. in total blood volume, 350 c.c. in plasma and 600 c.c. in cell volume. This was not a dilution process, since the cell plasma volume ratio tended to increase. In Case 6 (diabetic edema), simple hypervolemia was present in the edema period similar to that observed in Cases 1 and 2 in the cardiac group. Following diuresis, the blood volume decreased 1,050 c.c., a decrease of 600 c.c. in plasma, and 450 c.c.

19. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293-294 (July 28) 1923.

in cell volume. The percentage hemoglobin decreased 13 per cent. and the actual hemoglobin 26 per cent. This was a contraction process associated with both a water and actual hemoglobin decrease, with an excess loss of the latter. The percentage hemoglobin decrease was partially masked by a volume contraction, producing simple normovolemia. The normal cell plasma volume ratios were preserved. Only minor volume changes were noted during diuresis in all the cases of glomerular nephritis except Case 9, in which there was oligocythemic normovolemia in the edema period; during diuresis, the plasma volume decreased 970 c.c., whereas the cell volume increased 220 c.c., producing an oligocythemic hypovolemia, with a net decrease of 750 c.c. in the total blood volume. This may indicate a contraction mechanism, associated with an actual increase of circulating hemoglobin. This is an

TABLE 7.—*Absolute and Percentage Volume Changes During Diuresis* *

		Blood				Plasma				Cells			
		Increase		Decrease		Increase		Decrease		Increase		Decrease	
Case	Type of Edema	C.c.	Per Cent.	C.c.	Per Cent.	C.c.	Per Cent.	C.c.	Per Cent.	C.c.	Per Cent.	C.c.	Per Cent.
1	Cardiac	960	14.0	...	..	350	8	...	..	600	24	...	..
2	Cardiac	150	2.5	...	..	...	..	100	2	250	10	...	..
3	Cardiac	...	....	560	9	...	..	180	5	...	..	380	15
4	Diabetic	120	3.0	...	..		No change			110	6	...	..
5	Diabetic	420	7.0	...	..	900	25	...	..	...	..	470	20
6	Diabetic	...	....	1,060	15	...	..	610	14	...	..	450	17
7	Glomerular nephritis	...	....	100	3	150	6	...	..	...	..	250	20
8	Glomerular nephritis	...	....	280	6	...	..	410	2	120	12	...	..
9	Glomerular nephritis	...	....	750	19	...	..	960	27	210	48	...	..
10	Glomerular nephritis	150	5.0	...	..	310	14	...	..	...	..	160	21
11	Nephrosis		No change				No change				No change		
12	Nephrosis	...	....	110	1.5		No change			...	..	110	4
13	Nephrosis	...	....	140	2		No change			...	..	130	5
14	Nephrosis	...	....	610	10	...	..	420	9	...	..	190	14

* As calculated by the dye method.

interesting phenomenon, possibly revealing a recovery from anemia accomplished in two ways, by a contraction of the blood volume, and by an actual increase of the circulating hemoglobin. The blood volume shrinkage may be the result of an excessive plasma water removal, incident to diuresis, or it may be a natural compensatory process, having as its object a greater increase of percentage hemoglobin. In Case 5 (diabetic edema), there were simple normovolemia and abnormally high percentage hemoglobin, revealing increased blood concentration. Following a loss of 13 kg. of body weight, the plasma volume increased 900 c.c., the cell volume decreased 480 c.c., and there was a marked decrease in the cell plasma volume ratio by hematocrit, thus producing oligocythemic normovolemia. There was an actual loss of circulating hemoglobin of 300 gm. (27 per cent.), and a 32 per cent. decrease in percentage hemoglobin, revealing the production of a true anemia, with mild dilution of the blood. The cases of nephrosis (Cases 11, 12 and 13) revealed only minor volume fluctuations during the period of fluid

loss. In Case 14 (nephrosis with moderate anemia), there was a loss of 610 c.c. in total blood volume, 420 c.c. in plasma, and 190 c.c. in cell volume, indicating a progressive anemia associated with water loss. The volume contraction concealed the loss in actual hemoglobin, the percentage hemoglobin showing no change.

STUDIES ON BLOOD AND PLASMA COMPOSITION IN RELATION TO BLOOD CONCENTRATION (TABLES 3 AND 5)

The blood and cell water percentage in the edema period were variable, and bore a close relation to the hemoglobin content, rather than to the volume. The highest percentage of blood water, as would be expected because of the anemia, was found in the cases of glomerular nephritis. In a case of diabetic edema (Case 5) a moderate concentration of the blood and cells existed during the period of edema; following diuresis, a marked increase or restoration in the percentage water of the blood and cells took place, while the percentage plasma water decreased 1 per cent. In Case 13, following diuresis, a definite dehydration occurred in the cells and plasma.

In nine of the cardiac and renal cases (Cases 1, 2, 3, 8, 10, 11, 12, 13 and 14), the plasma water was relatively increased either in the edema or postedema period, showing the existence of hydremia. This was as infrequent, however, in the dry as in the edema period. In Cases 1 and 14, the plasma volumes were increased, but, as the plasma proteins were not determined, it is not known whether there was an actual protein loss or a dilution. In the other cases the relative plasma volumes were normal. Since hydremia was more common in hypovolemic than in hypervolemic states, it is evident that the percentage plasma water gives no information as to the circulating blood or plasma volume. In Case 13, a definite decrease in plasma water took place during diuresis, but no change in relative or absolute plasma volumes.

As a result of diuresis, the plasma water content varied slightly in all but one case (Case 12). The greatest fluctuations were observed in Case 1 (cardiac edema) and in Case 13 (nephrosis). In Case 1 there was a marked decrease in percentage plasma water with an increase in absolute blood and plasma volume. In Case 13, in which there was a plasma water decrease, no change occurred in plasma volume. In Cases 5, 6 and 9, in which the greatest plasma volume changes occurred with fluid loss, only slight changes occurred in plasma concentration.

The percentage cell water, according to the calculation hematocrit method, reveals great fluctuations. In Case 5, following fluid loss, a 13 per cent. increase in cell water, and a 32 per cent. decrease in hemoglobin were observed.

The percentage hemoglobin showed no constant value during edema except in cases of glomerular nephritis. The hemoglobin fluctuations during diuresis were not constant for any of the edemas. Considerable fluctuations in either direction were observed. In several cases, however, the hemoglobin revealed no change during diuresis.

The percentage hemoglobin changes were roughly proportionate to those of the cell volume, but not to those of the total volume. In Case 5, during diuresis, there was a 32 per cent. decrease in percentage hemoglobin, but the total blood volume increased only 9 per cent. The increase in plasma volume explains this disproportion.

In Case 2, a definite decrease of hemoglobin occurred, with a slight increase in total blood and cell volume. This finding is difficult to explain; however, the volume changes were not much greater than the possible error of the method used in their determination. In the majority of the cases in which the percentage hemoglobin did not change during the period of fluid loss, volume changes were slight or nil. The greatest fluctuations in either direction in percentage hemoglobin took place in the cardiac and diabetic edemas. The fluctuations in percentage hemoglobin do not accurately reflect the fluctuations in total blood volume (Cases 2, 5 and 8, Table 5). The fluctuations in plasma volume may entirely mask those of the cell volume. In Case 13 there was a loss in circulating hemoglobin of 8 per cent., with no change in percentage hemoglobin, the discrepancy being explained by a 10 per cent. decrease in the total blood volume.

COMMENT

The blood volume states in the small number of cases of edema in this series reveal a tendency to grouping of the different clinical types of edema. It should be recognized that the accuracy of the values relative to volume depend on the validity of the findings by the dye method. Simple hypervolemia predominated in the cardiac cases and in one case of diabetes in the edema stage. Hypovolemia was practically constant in the cases of glomerular nephritis, while normovolemia was the rule in the cases of nephrosis and diabetes. There is no absolute evidence that sufficient dilution occurred in the period of edema to produce oligocythemic hypervolemia, or to cause a relative or dilution anemia except, possibly, in one case of nephrosis complicated with chronic infection of bone (Case 14). Dilution processes in minor degrees were found in several instances following diuresis, apparently representing adjustments in the volume water solid balance following fluid loss. Oligocythemic hypervolemia is probably rare, and may represent a dilution condition resulting when the physiologic mechanisms fail to maintain the normal cell plasma volume ratio in the presence of an excess of blood water.

The blood was decreased in relation to body weight in the presence of obesity, and this relationship was maintained in the presence of edema in one case. The hypovolemia in cases of edema of glomerular nephritis is explained on the basis of anemia or decreased cell volume. The cell plasma volume relationship showed a tendency to maintain the normal ratio in the cases of cardiac disorders, diabetes and nephrosis, in both edema and nonedema periods. When this ratio was not maintained, anemia was present. Anemia is practically always associated with glomerular nephritis,[20] and therefore there was a decrease in cell plasma volume ratio in these cases, both in edema and nonedema periods. There was no evidence that dilution played a part in the anemia of glomerular nephritis. There were no uniform changes in the volume states during diuresis in the various types of edema. In the renal cases, minor fluctuations, if any, were observed in cell and plasma volumes. The greatest fluctuations were observed in the cardiac and diabetic cases. Changes took place in either direction, indicating volume contraction, mild dilution, or restoration and concentration processes.

The concentration values during the edema period were too variable to permit generalizations. Hydremia, or increased water content of the plasma, was found occasionally in all types of edema, in periods of edema and in periods free from edema. The highest concentration value was found in cardiac cases. No constant fluctuation occurred during the period of diuresis, and the changes were not uniform, occurring in either direction.

The cell water percentage fluctuated widely, which possibly explains the slight variations observed in the cell percentage by hematocrit. The fluctuations in percentage hemoglobin do not always reflect changes in the total blood volume, as plasma volume variation may partially mask the fluctuation in actual hemoglobin and cell volume.

SUMMARY

In a small series of cases representing different types of edema, the blood was studied in relation to the circulating total blood and plasma volume and its composition in both edema and postedema periods.

Because of the confusion and inadequacy of terms relating to volume states, certain new terms are proposed. In the edema stage, an increased total circulating blood volume, simple hypervolemia was observed in certain of the cardiac and diabetic cases, but not in any case of edema of renal origin. No definite evidence was obtained to show that oligocythemic hypervolemia exists as a maintained state in edema, except possibly in the presence of a true anemia. A decreased blood volume

20. Brown, G. E., and Roth, Grace M.: The Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817-840 (Dec.) 1922.

with a decreased cell to plasma volume ratio, oligocythemic hypovolemia, was found in the four cases of glomerular nephritis. This is explained on the basis of the existing anemia, and apparently stands in no relation to the edema itself. The anemia is a true or absolute anemia and is not due to dilution. Simple normovolemia was found in all three uncomplicated cases of nephrosis.

Studies of the composition of the blood revealed no fixed relationship between hydremia (increased percentage plasma water) and the volume state. Diuresis exercises no fixed influence on the volume and composition of the blood. Only minor changes characterize the disappearance of edema of renal origin and are probably, in some instances, related to compensatory efforts of the blood to establish normal cell plasma volume ratios. The cases of renal edema show the least fluctuation during diuresis.

During diuresis, marked changes in blood volume were observed in certain cases of edema of cardiac or diabetic origin, representing variable adjustments in volume, solids and fluid factors. In diuresis the percentage fluctuation in any one constituent of the blood does not necessarily reflect corresponding volume changes. Changes in blood solids may be partially or completely masked by fluctuation in water content in the absence of volume changes.

Book Reviews

MANAGEMENT OF DIABETES. By GEORGE A. HARROP, JR. Pp. 176. Price, $2.00. New York: Paul B. Hoeber, 1924.

Since insulin has become important in the treatment of diabetes, a manual containing instructions in directing its use, along with dietary regulations, is needed by the general practitioner. Such information, given with sufficient detail, is contained in this book by Harrop.

There are discussed the metabolic derangement in diabetes; the acid base mechanism and the acidosis of diabetes; insulin and its physiologic effects in the body; the management of the diabetic patient with insulin and diet regulation, and the treatment of acidosis, as well as other complications of diabetes.

The instructions regarding diet regulation include useful recipes and food value tables. Methods are given for determining the alkali reserve and sugar of the blood, as well as qualitative and quantitative tests for sugar and other urine constituents.

The text is a useful guide for the general practitioner, and may be given for instruction to intelligent patients.

CLINICAL LABORATORY DIAGNOSIS. By ROGER SYLVESTER MORRIS. Pp. 456; 5 plates; 99 illustrations. New York: D. Appleton & Co., 1923.

This is an excellent, well illustrated text for clinical laboratory examinations, considerably more extensive than the 1913 volume. It contains detailed instructions for conducting qualitative and quantitative examinations of the dissolved urine constituents, as well as for the identification of the formed elements. The same is true as regards examinations of the gastric juice, the feces and the sputum. Much useful information regarding the identification of parasites, both vegetable and animal, is included. Bacteriologic methods for identifying organisms of the mouth, eye, throat and nose are given, as well as those necessary for recognizing the vegetable and animal parasites of the skin.

The chapter dealing with blood examinations contains instructions for determining the cell content, the hemoglobin and certain ratios, such as the volume and color indexes, the viscosity, the coagulation time, the specific gravity and the fragility of red cells. The instructions for identifying the cells in stained preparations are complete. There are given descriptions of the changes in the blood with different diseases and the identification of blood parasites. The culturing of the blood for bacteria, and directions for determining, quantitatively, the chemical constituents are included. There are other instructions for examining spinal fluid and fluids from serous cavities.

This is a well organized and useful laboratory manual.

QUESTIONS ACTUELLES DE BIOLOGIE MÉDICALE. Par G. H. ROGER, Doyen de la Faculté de médicine de Paris, Professeur de Pathologie expérimentale et comparée, Membre de l'Académie de Médicine. Paris: Masson et Cie, 1924.

This monograph is essentially a summary of the author's own researches on the lungs, the cardiovascular system, the suprarenals, the liver, the ferments and the bile. Each of these subjects is treated in a separate chapter. The author has made special investigations on the action of the lung on the fatty substances of the blood, and concludes that the lung tissues have a very marked lipolytic action.

The chapter on cardiovascular physiology and pathology deals particularly with experiments with injections of organ extracts.

In the chapter on the suprarenal glands, the author details experiments which lead him to conclude that the suprarenal medulla secretes epinephrin continuously in quantities sufficient to counterbalance the influence of the vagi nerves on the heart.

In the chapter on the rôle of the bile, the author concludes among other things, that bile retards intestinal putrefaction by three processes: that is, it favors the development of *B. coli* and depresses the development of anaerobic organisms; it diminishes the secretion of ferments by the bacteria, and it decreases the action of these bacterial ferments on fermentable material.

There are very few references to the literature in the monograph, and no index.

APERCU DE LA PHYSIOLOGIE ET DE LA PATHOLOGIE GENERALES DU SYSTEME LACUNAIRE. Par C. ACHARD, Professor de clinique médicale à la Faculté de médecine de Paris; Membre de l'Académie de médecine. Pp. 125. Paris: Masson et Cie, 1924.

This monograph is a critical and useful review of the physiology and pathology of what the author calls, the "système lacunaire." Under this term, the author includes: the great variety of spaces in the body, such as the intercellular spaces; the lymph spaces in the connective tissues; the subarachnoid spaces; the spaces in the internal ear containing endolymph and perilymph; the spaces in the eye containing the aqueous and vitreous humor; the serous cavities of the body, and the spaces in the joints containing synovial fluids, as well as the fluids in these varieties of spaces, and the physiology of the modification of these fluids in diseases such as edema, glaucoma, hydrocephalus and inflammations. The author points out the primitive character of this system of tissue spaces, this system antedating, both in phylogeny and autogeny, the vascular and the true lymphatic systems.

In the last chapter, the author discusses the therapeutic measures for the control of the various types of edema and excess accumulation of fluids in the lacunaire système.

The appendix contains analyses of the chemical composition of all these various fluids in health, and in many cases as modified by various diseases.

The literature cited is mainly French and German. The author refers to only two English and twelve American contributions in this field. Research men and internists interested in the fundamental problems of hydration, dehydradration, edema, etc., will find the volume interesting and helpful.

DISEASES OF THE CHEST AND PRINCIPLES OF PHYSICAL DIAGNOSIS. By GEORGE W. NORRIS, M.D., Professor of Clinical Medicine in the University of Pennsylvania, and HENRY R. M. LANDIS, M.D., Director of the Clinical and Sociological Departments of the Henry Phipps Institute of the University of Pennsylvania. With a chapter on the Electrocardiograph in Heart Disease, by EDWARD KRUMBHAR, PH.D., M.D., Director of Laboratories of the Philadelphia General Hospital. Cloth. Price, $9.50 net. Third edition, revised. Pp. 907; 432 illustrations. Philadelphia: W. B. Saunders Company, 1924.

The third edition has been revised and enlarged. It is a book of 907 pages, attractively printed and adequately illustrated. Some parts have been rewritten and the descriptions of a number of rare conditions, formerly omitted, are included. The work is too well known among medical educators to require detailed description. The numerous illustrations of frozen sections of the normal and of the grossly pathologic chest, showing the relationship of deep structures as well as of surface anatomy, are especially valuable. The chapter on the electrocardiograph is a clear and concise presentation without undue emphasis on this rather technical phase of physical diagnosis. In fact, the importance

of established means of physical diagnosis as compared with modern laboratory methods, without, however, detracting from the usefulness of the latter, is stressed throughout the book.

Parts I and II are concerned with the examination, and Parts III and IV with diseases of the respiratory and circulatory systems, respectively. Since the special parts include etiology, bacteriology, morbid anatomy, and symptomatology of diseases of the chest, the scope of the work necessarily overlaps the fields both of physical diagnosis and general medicine. The book is among the best texts in English on diseases of the chest; it is chiefly of value, however, as a text on physical diagnosis. That there is a demand for a book of this type is evidenced by the fact that it has gone through three editions in seven years. Practitioners of medicine undoubtedly find it a useful treatise on diseases of the chest.

From the standpoint of the medical student, the book does not meet the requirements of an ideal text on physical diagnosis. It is not possible for him to use the present volume exclusively, even in its restricted field. For example, about two-thirds of the present volume, i. e., Parts III and IV, deal with the principles of medicine — etiology, pathology, symptomatology, etc.— as restricted to diseases of the chest. Much of the material would be better covered in a general test on the principles and practice of medicine. Moreover, physical diagnosis as applied to the head, abdomen and extremities is not included. While these are admittedly of less importance, an ideal text for students should include them.

The idea suggests itself that it would be a valuable contribution to medical education in this country if future editions of this excellent work could be restricted to the field of physical diagnosis, without necessarily shortening it. The ideal text in English on physical diagnosis remains to be written.

LECTURES ON ENDOCRINOLOGY. By WALTER TIMME, M.D., Attending Neurologist, Neurological Institute, New York; Professor of Endocrinology, Broad Street Hospital; Professor of Nervous and Mental Diseases, Polyclinic Medical School and Hospital. Price, $1.50. Pp. 123; 27 illustrations. New York: Paul B. Hoeber, 1924.

This little booklet is a reprint of an article published, in 1921, in the *Neurological Bulletin*. It contains chapters on the thymus gland, the pineal gland, the thyroid gland, the suprarenal glands, the pituitary gland and the gonads, together with a small number of references to the literature (six pages), and a brief index. The diction is concise and clear, the illustrations (photographs of patients) are on the whole, well selected; but the author frequently fails to distinguish clearly between theories and facts. Perhaps this is not so easily done in treating of the difficult subject of endocrinology in such a brief space. Naturally, the author stresses particularly the nervous manifestations of ductless gland disorders, or alleged ductless gland disorders, not always clearly showing which is cause and which is effect. The author accepts, apparently in toto, the current theories of the "vagotonia" and "sympathicotonia." He states, "Theoretically, the thymus secretes a substance which has vagotonic properties, and practically this is frequently found to be borne out." So far from actually being found frequently or infrequently it is still an open question how or whether the thymus actually functions as an endocrine gland. Certainly the extirpation of the thymus, in young animals, gives no support to the endocrine function theory of the thymus. According to Timme, persons with precocious involution of the thymus "are themselves precocious, with much initiative, are easily aroused to anger, and are resentful. They have cruel instincts and show little inhibition. Although they seem far advanced for their years while still young, they never seem thoroughly to mature, and become blocked in early adolescence. They seem to retain their impulsive, unreasoning characteristics, brook no restraint, and remain con-

stantly a prey to their easily aroused anger." This seems a big indictment against the thymus, on the basis of what is actually known of the function of this gland, at present.

In the chapter on the thyroid gland, the author states that "ammonium carbonate is converted finally into urea by parathyroid action." But where is the evidence for this interesting statement? The author ascribes the symptoms of the normal and artificial menopause in women to hyperthyroidism. "A good example of such hyperthyroidism is that seen in some women after the menopause — the ovarian function having ceased, the thyroid is left without sufficient counterbalance and a hyperthyroid state ensues. This awakens overactivity of the adrenals, with resulting high blood pressure; and the combination produces the flushing, the vasomotor instability, the paresthesiae, etc., of this condition." The control or inhibition of the thyroid by the gonads is still an unproved assumption, and there is no reliable evidence that the nervous manifestations of the menopause are due, in whole or in part, to excessive activity of the thyroid. Certainly, castration or spaying in animals does not lead to hyperthyroid symptoms, if we can rely on the basal metabolism as an index of thyroid activity.

In the chapter on the suprarenals, the author assumes that excessive blood pressure or hypertension is caused by excessive activity of the suprarenal medulla, and that the function of the suprarenal cortex is that of inhibition, or regulation of the output of epinephrin by the medulla. These are interesting speculations of working hypotheses, but can hardly as yet be put out as conclusions to guide the practitioner in diagnosis and treatment.

In the chapter on the gonads, the author says, "During the period following menstruation when the corpora lutea are formed, there is usually a diminished thyroid activity. As this period of luteal activity begins to wane, and the next menstrual period approaches, the thyroid, presumably less opposed, becomes overactive and the nervousness, excitability and general mental uneasiness produced by thyroid activity become manifest." This assumption of thyroid hyperactivity and hypo-activity, in certain periods of the menstrual cycle, is not borne out by basal metabolism studies.

In the preface to the booklet, the author says he has in mind the production of a larger and more complete work on this subject. In this larger work contemplated, it is to be hoped that the author's facile expression and clear diction will be coupled with greater critical analysis, both of the clinical and the experimental data in this difficult field.